Original article

Prevalence and prognostic implications of malnutrition as defined by GLIM criteria in elderly patients with heart failure

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SUMMARY

Background & aims: Although the Global Leadership Initiative on Malnutrition (GLIM) proposed a consensus scheme for diagnosing malnutrition in adults in clinical settings globally, the prevalence and prognostic value of malnutrition defined by GLIM criteria have yet to be evaluated in elderly patients with heart failure. This study aimed to determine the prevalence and prognostic implication of malnutrition as defined by GLIM criteria in comparison to those for a pre-existing definition of malnutrition, the geriatric nutritional risk index (GNRI), in elderly patients with heart failure
Methods: We evaluated malnutrition by two metrics, the GLIM criteria and geriatric nutritional risk index (GNRI), in 890 hospitalized patients with decompensation of heart failure aged ≥65 years, able to ambulate at discharge. The primary outcome was all-cause death within 1 year of discharge.
Results: According to GLIM criteria and GNRI <92, 42.4% and 46.5% of participants, respectively, had malnutrition, with moderate agreement (Cohen's kappa coefficient: 0.46 [95% confidence interval: 0.40 −0.51]). During 1 year of follow-up, 101 (11.4%) deaths were observed, and malnutrition defined by either the GLIM criteria or GNRI was associated with a higher mortality rate, independent of other prognostic factors (GNRI: hazard ratio, 1.45, P = 0.031; GLIM: hazard ratio, 1.57, P = 0.016). Although malnutrition defined by either criterion showed additive prognostic value when added to a model incorporating pre-existing prognostic factors, defining malnutrition by GLIM criteria instead of the GNRI yielded a statistically significant improvement in model prognostic predictive ability (net-reclassification improvement, 0.44, P < 0.001; integrated discrimination index, 0.013, P < 0.001).

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Conclusions: In elderly patients with heart failure, 42.4% are malnourished according to the GLIM criteria, which is associated with a poor prognosis, independent of known prognostic factors.
Clinical trial registration: University Hospital Medical Information Network (UMIN-CTR, https://www. umin.ac.jp/ctr/index.htm, study unique identifier: UMIN000023929)
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1. Introduction

Malnutrition is associated with prolonged hospital stays and mortality in patients who require hospitalization [1,2], and several tools have been developed to evaluate the nutritional status of patients [3]. Additionally, several groups and societies have proposed a variety of nutritional assessment criteria; however, the lack of consensus regarding diagnostic criteria for applications in clinical settings renders it difficult to compare the impact of malnutrition on patient prevalence and mortality in different populations [4–6]. Although malnutrition is an important and independent risk factor for morbidity and mortality in patients with heart failure [7], its reported prevalence and prognostic implications have varied widely, mostly due to differences in the tool used for the diagnosis of malnutrition [3]. Recently, the Global Leadership Initiative on Malnutrition (GLIM), which engaged several clinical nutrition societies with global reach, proposed a consensus scheme for diagnosing malnutrition in adults in clinical settings on a global scale [8]. However, the prevalence and prognostic value of malnutrition as defined by the GLIM criteria have yet to be clarified in elderly patients with heart failure. Therefore, this study aimed to determine the prevalence and prognostic implication of malnutrition as defined by GLIM criteria in comparison to those for a pre-existing definition of malnutrition, the geriatric nutritional risk index (GNRI), in elderly patients with heart failure.

2. Materials and methods

2.1. Study design and patient population

We conducted a post-hoc analysis of data from the FRAGILE-HF cohort study, which included 1332 hospitalized patients with decompensation of HF aged ≥65 years, who could ambulate at discharge. The design and main results of the FRAGILE-HF study have been published elsewhere [9]. Briefly, the main objective of the FRAGILE-HF study was to evaluate the prevalence and prognostic impact of multi-frailty domains in elderly patients with heart failure who required hospitalization. Exclusion criteria were as follows: (1) previous heart transplantation or treatment with a left ventricular assist device, (2) on either chronic peritoneal dialysis or hemodialysis, and (3) acute myocarditis. Patients with missing brain natriuretic peptide (BNP) or N-terminal-proBNP data, and patients with a BNP level <100 pg/mL or N-terminal-proBNP level <300 pg/mL at admission, were also excluded as the diagnosis could be unclear. Patients with reduced and preserved ejection fraction were both enrolled. Fifteen hospitals in Japan enrolled patients from September 2016 to March 2018.

All participants were notified regarding their participation in the study, and it was explained that they were free to opt-out of participation at any time. The study was conducted in compliance with the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. Since this was an observational study without invasive procedures or interventions, written informed consent was not required under the Ethical Guidelines for Medical and Health Research Involving

Human Subjects, issued by the Japanese Ministry of Health, Labor, and Welfare. The study protocol was approved by the ethics committee of each participating hospital. Study information, including the objectives, inclusion and exclusion criteria, primary outcome, and names of the participating hospitals, were published in the publicly available, University Hospital Medical Information Network (UMIN-CTR, unique identifier: UMIN000023929), before the first patient was enrolled.

2.2. Definition of malnutrition according to the GLIM criteria and GNRI

According to the GLIM criteria, we defined malnutrition using a two-step approach, as strongly recommended by the GLIM consensus statement [10]. First, we applied the Malnutrition Universal Screening Tool (MUST) [11], which is one of the screening tools recommended by the GLIM consensus paper, to screen for patients at risk using data obtained before discharge. Patients with a MUST score ≥1 were considered at-risk for malnutrition according to the two-category criteria. Subsequently, patients at-risk for malnutrition according to MUST criteria were evaluated using the GLIM criteria. The GLIM criteria comprise three phenotypic and two etiological components for the diagnosis of malnutrition, and at least one criterion from each component must be met to diagnose malnutrition. Regarding the phenotypic criteria, we inquired about body weight changes occurring within the past one year (which is one of the suggested thresholds), with consideration of the fluctuations in body weight in patients with heart failure. Additionally, reduced muscle mass was defined by the appendicular skeletal mass index, measured by a biometric impedance analysis (BIA) using cutoffs for the Asian populations, as proposed by the Asian Working Group for Sarcopenia (7 kg/m^2 for males and 5.7 kg/m^2 for females) [12]. As the safety of performing BIA in patients with a cardiac implantable electronic device remains an open discussion, such patients did not undergo BIA and were excluded from the analysis. Also, BMI<18.5 kg/m^2 for age <70 years and <20 kg/m^2 for age >70 years were used as one of the phenotypic criteria. Regarding the etiologic criteria, all patients are diagnosed with heart failure, which is listed as one of the diseases associated with chronic or recurrent mild-to-moderate inflammation.

Patients were prospectively followed up for 1 year after discharge. After discharge, most patients were followed up in outpatient clinics at least every 3 months, as well as according to their medical needs. For those without follow-up visits in our clinics, prognostic data were obtained from the medical records of other medical facilities caring for the patient, or from the family, via telephone interviews.

The GNRI was calculated using the following formula: 1.489 × serum albumin (g/L) + 41.7 × (body weight in kilograms/ideal body weight) [13]. The ideal body weight was calculated using the formula: 22 × the square of the height in meters. We defined a patient as malnourished if his/her GNRI was <92. The cutoff of 92 was selected because malnutrition defined according to this cutoff has been shown to be associated with prognosis in numerous studies on

heart failure, regardless of the left ventricular ejection fraction [14–16].

2.3. Statistical analysis

Normally distributed continuous variables are expressed as the mean ± standard deviation, while non-normally distributed variables are presented as the median and interquartile range. Categorical variables are expressed as numbers and percentages. The cohort was classified into groups based on malnutrition according to the GLIM criteria, as well as according to the GNRI. Group differences were evaluated using one-way analysis of variance or the Kruskal–Wallis test for continuous variables, and the chi-squared or Fisher's exact test for dichotomous variables, as appropriate.

Survival was evaluated using the Kaplan–Meier method, and compared with log-rank statistics. The primary outcome was all-cause death, and the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and (log-transformed) BNP levels at discharge were used as adjustment variables in the multivariable prognostic models for the outcome of all-cause death, as the MAGGIC score is a well-validated risk score for Japanese patients with heart failure [17]. The MAGGIC risk score is the score based on 13 independent predictors of long-term mortality including age, gender, systolic blood pressure, LVEF, body mass index, creatinine level, New York Heart Association class, diabetes mellitus, chronic obstructive pulmonary disease, current smoker, diagnosis of HF in the past 18 months, and not taking BB, ACE-I, or ARB. Multiple imputation was used to take into account missing covariate data in constructing the multivariable Cox regression models. We created 20 datasets using a chained-equations procedure [18]. Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result, using the method described by Barnard and Rubin [19].

To evaluate the additive prognostic predictive value of the two malnutrition metrics, we constructed the following three models for 1-year all-cause mortality: MAGGIC score + log BNP; MAGGIC score + log BNP + malnutrition defined by the GNRI <92; and MAGGIC score + log BNP + malnutrition defined by the GLIM criteria. Receiver operator characteristic (ROC) curves, and their areas under the curve (AUCs), were evaluated, and confidence intervals (CIs) of the AUCs were obtained via bootstrap resampling (2000 samples). AUCs were compared using the Wald test, based on the empirical standard deviation obtained via resampling (2000 samples). We also calculated the continuous net-reclassification improvement (NRI) and integrated discrimination index (IDI), with the corresponding 95% CIs, to evaluate the incremental prognostic predictive ability of the two malnutrition metrics [20].

A two-tailed p < 0.05 was considered to indicate statistical significance in all analyses. Statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org).

3. Results

Among 1332 evaluated patients registered in the FRAGILE-HF study, 261 patients were excluded due to missing data on either body weight changes within 1 year, baseline body mass index (BMI), or baseline serum albumin level. Additionally, 181 patients were excluded because they were unable to undergo BIA due to an implanted cardiac device (e.g. a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy defibrillator/pacemaker) or simply had missing data. The remaining 890 patients were analyzed. We compared the prognosis

between included and excluded patients, and no difference in prognosis was observed (log-rank: P = 0.26).

Patient characteristics stratified by malnutrition as defined by the GLIM criteria and GNRI are shown in Table 1. Overall, 42.4% and 46.5% of participants were defined as malnourished according to the GLIM criteria and GNRI, respectively. These two malnutrition metrics showed moderate agreement, with a Cohen's kappa coefficient of 0.46 (95% CI: 0.40–0.51). Malnutrition as defined by the GLIM criteria was associated with older age, lower BMI, lower blood pressure, and less frequent history of hypertension. Regarding biomarkers, lower albumin, creatinine, and sodium levels were associated with malnutrition as defined by the GLIM criteria. The associations of malnutrition as defined by the GNRI showed some similarities to those for malnutrition as defined by GLIM criteria, but some differences were observed. More frequent New York Heart Association (NYHA) class III/IV, less frequent history of atrial fibrillation and diabetes, fewer prescriptions of beta-blockers, and higher BNP levels were associated with malnutrition as defined by the GNRI, but not with malnutrition as defined by the GLIM criteria.

The rate of 1-year follow-up completion was 97.9%, and prognostic data were available for 871 patients. During the 1-year follow up, 101 (11.4%) deaths were observed, with significantly more deaths among patients malnourished, as defined by either criterion, than in those without malnutrition (GLIM criteria: 15.3% vs. 8.9%, P = 0.004; GNRI: 16.4% vs. 7.4%, P < 0.001). Kaplan–Meier curves showed a statistically higher event rate in patients malnourished than in those without malnutrition, by either definition (GLIM criteria: log-rank P = 0.003; GNRI: log-rank P < 0.001) (Fig. 1). In unadjusted and adjusted Cox regression analyses, malnutrition as defined by either the GLIM criteria or a GNRI was significantly associated with a poor prognosis, even after adjustment for the MAGGIC score and log-transformed BNP (Table 2). The proportional hazards assumption for Cox regression was checked by an analysis of the scaled Schoenfeld residuals, and no violation was found for any variables, as well as for the global test of the whole model, using both the GLIM criteria and GNRI (P > 0.10 for all). The results of the three planned logistic models for 1-year mortality are shown in Table 3. AUCs were 0.72 (95% CI: 0.68–0.77), 0.72 (95% CI: 0.68–0.77), and 0.74 (0.68–0.80) for MAGGIC score + log BNP, MAGGIC score + log BNP + malnutrition defined by the GNRI, and MAGGIC score + log BNP + malnutrition defined by the GLIM criteria and no significant difference in the AUCs of the ROC curves was found. However, adding the presence/absence of malnutrition as defined by either the GNRI or GLIM criteria to the baseline model was associated with significant NRI, but the IDI was significant only for malnutrition based on the GLIM criteria and not the GNRI. Moreover, we found that switching the definition of malnutrition from the GNRI to the GLIM criteria yielded a statistically significant improvement in the prognostic predictive ability of the model (NRI: 0.44, P < 0.001; IDI: 0.013, P < 0.001).

4. Discussion

To the best of our knowledge, the present study is the first to show that 42.4% and 46.5% of hospitalized elderly patients with heart failure, who are able to ambulate, are malnourished according to the GLIM criteria and the GNRI, respectively. Although these values are not very different, there was only moderate agreement between the two metrics of malnutrition. Of note, although malnutrition defined by either metric was independently associated with a poor prognosis, malnutrition as defined by the GLIM criteria was associated with better prognostic prediction compared to GNRI when it was added to pre-existing prognostic factors.

The reported prevalence of malnutrition and being at-risk of malnutrition in patients with heart failure varies widely, from 16%

Table 1
Patient characteristics stratified by malnutrition as defined by the GLIM criteria and GNRI.

Variables	GLIM criteria		P value	GNRI		P value
	With malnutrition N = 378	Without malnutrition N = 512		With malnutrition N = 414	Without malnutrition N = 476	
Age (years)	82 [75,86]	79 [73,85]	0.001	82 [76,87]	78 [72,84]	<0.001
Male sex (%)	217 (57.4)	304 (59.4)	0.603	232 (56.0)	289 (60.7)	0.179
BMI	19.6 ± 3.1	23.7 ± 3.1	<0.001	19.6 ± 2.5	24.0 ± 3.4	<0.001
ASMI (kg/m^{-2})	6.89 ± 1.58	7.86 ± 1.95	<0.001	6.99 ± 1.77	7.75 ± 1.82	<0.001
NYHA Class III/IV (%)	48 (12.7)	61 (11.9)	0.803	60 (14.5)	49 (10.3)	0.071
Systolic blood pressure (mmHg)	113 ± 17	115 ± 17	0.035	115 ± 17	114 ± 17	0.365
Diastolic blood pressure (mmHg)	61 ± 11	64 ± 11	<0.001	61 ± 11	64 ± 11	<0.001
Heart rate (bpm)	71 ± 14	71 ± 14	0.852	71 ± 14)	71 ± 14	0.939
Heart failure phenotypes (%)			0.533			0.363
HFrEF	157 (41.9)	194 (38.1)		154 (37.4)	197 (41.7)	
HFmrEF	64 (17.1)	93 (18.3)		73 (17.7)	84 (17.8)	
HFpEF	154 (41.1)	222 (43.6)		185 (44.9)	191 (40.5)	
LVEF (%)	45 ± 17	47 ± 16	0.244	47 ± 17	45 ± 16	0.094
Comorbidities (%)						
Atrial fibrillation	162 (42.9)	232 (45.3)	0.509	158 (38.2)	236 (49.6)	0.001
Coronary artery disease	127 (33.6)	188 (36.7)	0.373	144 (34.8)	171 (35.9)	0.776
COPD	41 (10.8)	57 (11.1)	0.979	49 (11.8)	49 (10.3)	0.532
Diabetes	128 (33.9)	193 (37.7)	0.269	124 (30.0)	197 (41.4)	0.001
Hypertension	254 (67.2)	388 (75.8)	0.006	293 (70.8)	349 (73.3)	0.441
History of heart failure			0.048			0.240
None	200 (52.9)	230 (44.9)		206 (49.8)	224 (47.1)	
Less than 18 months	53 (14.0)	75 (14.6)		65 (15.7)	63 (13.2)	
More than 18 months	125 (33.1)	207 (40.4)		143 (34.5)	189 (39.7)	
Prescription at discharge (%)						
Loop diuretics	214 (56.6)	270 (52.7)	0.280	230 (55.6)	254 (53.4)	0.556
ACE-I/ARB	256 (67.7)	365 (71.3)	0.284	277 (66.9)	344 (72.3)	0.096
Beta blocker	283 (74.9)	386 (75.4)	0.920	295 (71.3)	374 (78.6)	0.015
MRA	36 (9.5)	38 (7.4)	0.317	39 (9.4)	35 (7.4)	0.321
Lab data at discharge						
Hemoglobin (g/dL)	11.8 ± 2.0	12.1 ± 2.1	0.109	11.3 ± 1.8	12.5 ± 2.1	<0.001
Albumin (g/dL)	3.4 ± 0.5	3.6 ± 0.5	<0.001	3.2 ± 0.4	3.8 ± 0.4	<0.001
Creatinine (mg/dL)	1.29 ± 0.67	1.41 ± 0.81	0.013	1.39 ± 0.88	1.33 ± 0.64	0.195
BUN (mg/dL)	26 [19,34]	25 [19,35]	0.961	25 [19,34]	26 [19,35]	0.982
eGFR (mL/min/1.73m^2)	55 ± 21	53 ± 22	0.091	53 ± 22	55 ± 21	0.177
Sodium (mEq/L)	139 ± 4	140 ± 4	<0.001	140 ± 4	139 ± 4	0.251
BNP (pg/mL)	286 [152,506]	240 [124,456]	0.060	313 [154,563]	233 [117,419]	<0.001

Plus−minus values are means ± standard deviation and numbers with square brackets are median and interquartile range. Numbers in brackets are percentage.
ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; ASMI, appendicular skeletal muscle mass index; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
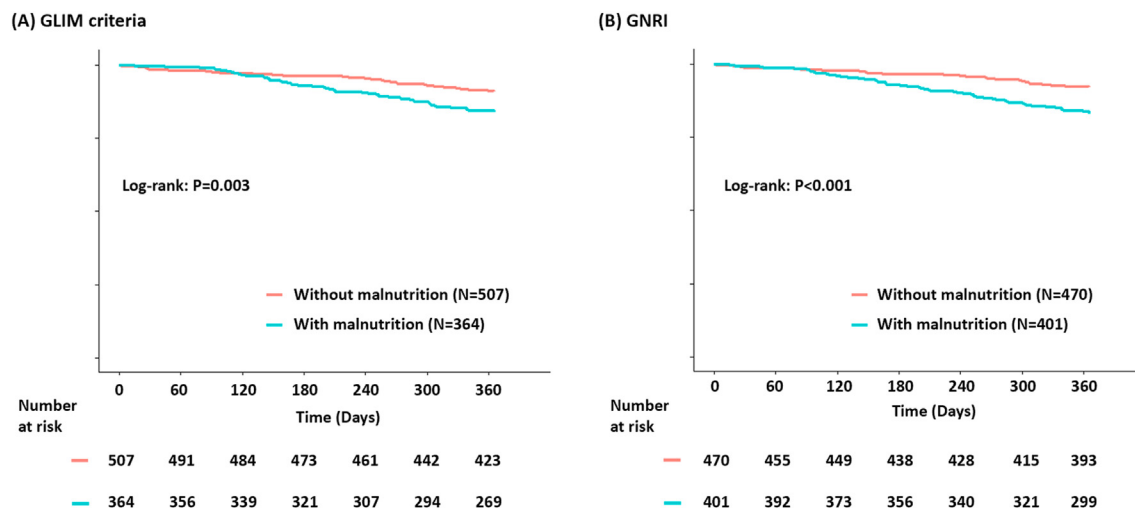

Fig. 1. Kaplan−Meier curves for 1-year all-cause mortality stratified by the presence/absence of malnutrition as defined by (A) the GLIM criteria and (B) GNRI. GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index.

Table 2
Unadjusted and adjusted Cox regression analyses for all-cause mortality.

Variables	GLIM criteria						GNRI					
	Unadjusted Cox model			Adjusted Cox model			Unadjusted Cox model			Adjusted Cox model		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Malnourishment	1.86	1.28–2.69	0.001	1.57	1.09–2.27	0.016	2.08	1.49–2.94	<0.001	1.45	1.03–2.04	0.031
MAGGIC score (per 1-point increase)				1.11	1.08–1.14	<0.001				1.11	1.08–1.14	<0.001
Log BNP				1.46	1.23–1.73	<0.001				1.43	1.21–1.70	<0.001

BNP, brain natriuretic peptide; CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; HR, hazard ratio; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure.

Table 3
Model improvement with the addition of information on malnutrition as defined by the GLIM criteria and GNRI.

		Updated model	
		MAGGIC score + Log BNP + Malnutrition$_{GNRI}$	MAGGIC score + Log BNP + Malnutrition$_{GLIM}$
Baseline model	MAGGIC score + Log BNP (AUC: 0.72, 95%CI: 0.68-0.77)	AUC$_{comparison}$: P=0.576 NRI: 0.35 [0.18 - 0.52], P<0.001 IDI: 0.003 [-0.001-0.008], P=0.131	AUC$_{comparison}$: P=0.491 NRI: 0.38 [0.17 - 0.60], P<0.001 IDI: 0.016 [0.008-0.023], P<0.001
	MAGGIC score + Log BNP + Malnutrition$_{GNRI}$ (AUC: 0.72, 95%CI: 0.68-0.77)		AUC$_{comparison}$: P=0.780 NRI: 0.44 [0.23 - 0.64], P<0.001 IDI: 0.013 [0.006-0.02], P<0.001

to 90% [3,21]. This variation is partially attributable to differences in the characteristics of the patients included in each study; however, differences in the criteria used to define malnutrition comprise another major reason for the variation. Indeed, Sze et al. showed that the prevalence of malnutrition varied from 8% (using the Prognostic Nutritional Index [PNI]) to 54% (using the Controlling Nutritional Status [CONUT]) in the same heart failure cohort, depending on the tool used to define malnutrition [22]. Therefore, a universally accepted definition of malnutrition that has a strong association with the prognosis is needed for both clinical practice and scientific research. Moreover, the lack of a universal definition of malnutrition hampers researchers from comparing the prevalence of malnutrition between heart failure and other diseases. Since GLIM criteria were proposed as a consensus scheme for diagnosing malnutrition in adults in clinical settings globally, several previous studies investigated malnutrition based on the GLIM criteria in patients with diseases other than heart failure. For example, Fiorindi et al. reported that 42% of patients with inflammatory bowel disease who required surgical procedures were malnourished according to the GLIM criteria [23]. Additionally, 24% of patients with lung cancer [24] and 25.8% of patients with hematologic malignancy [25] were diagnosed with malnutrition by the GLIM criteria. Although the prevalence of malnutrition in our heart failure cohort seems higher than that in these other diseases (reinforcing the importance of malnutrition in patients with heart failure), the prevalence could still be underestimated, as we did not include patients with heart failure who were unable to ambulate. As such patients are likely to be old and have low BMI, the true prevalence of malnutrition could be even higher. However, this speculation should be clarified in future studies.

In the present study, we evaluated the prognostic value of malnutrition as defined by the GLIM criteria and showed its additive prognostic value over that for pre-existing risk factors. We also compared the GLIM criteria and the GNRI in terms of prognostication, and found that applying GLIM criteria to identify those malnourished might be associated with better prognostic prediction compared to using GNRI when the information was added to pre-existing risk model. The GNRI is one of the major malnutrition metrics used to evaluate the nutritional status in several diseases, including heart failure, and numerous studies have shown that malnutrition according to the GNRI is strongly associated with mortality [14–16]. In the present study, we did not compare the GLIM criteria to other malnutrition metrics, such as the CONUT score, PNI, and Mini-Nutritional Assessment (MNA), in terms of prognostication. However, in a study that included 4021 hospitalized patients with heart failure [22], the GNRI, in comparison with the CONUT score and PNI (the GLIM criteria was not evaluated), showed the best additive prognostic value when added to a baseline model encompassing known risk factors. The GNRI consists of two factors: the BMI and serum albumin level. Although albumin is an important metric of nutrition, its synthesis is regulated by other factors, including serum oncotic pressure, inflammation, and volume status, in patients with heart failure. Thus, one possible explanation for the difference in prognostic value between the GLIM criteria and GNRI is the multitude of processes in heart failure that alter the level of albumin, rendering the albumin level as an unspecific marker of malnutrition. This may be especially true for patients who require hospitalization due to an exacerbation of heart failure, in which a number of states other than nutritional status could alter the serum albumin concentration. For instance, previous studies have shown an association between hypoalbuminemia and volume overload in patients with heart failure [26–28]. This could be supported by our finding that those with malnutrition defined by GLIM are associated with significantly lower creatinine levels compared to the levels noted in those without malnutrition, which was not observed when GNRI was

used to define malnutrition even though those with malnourishment showed significantly lower BMI in both definitions. Given that creatinine levels can be low in those with smaller muscle mass, which is a good indicator of malnutrition, no significant difference in creatinine levels between GNRI groups may reflect the association between lower GNRI and more impaired renal dysfunction. As albumin can be influenced by many factors, it might not be a good indicator of nutritional status even though it is associated with prognosis. Indeed, consensus statements questioned the utility of albumin as a nutrition assessment tool and this implies that the validity of using nutrition assessment tools including albumin especially for patients with heart failure should be taken seriously [5,6]. As the GLIM criteria do not include the albumin level as a component, instead using directly measured muscle mass, it might more specifically reflect the nutritional status, especially in patients with heart failure, resulting in an additive prognostic value that cannot be obtained otherwise.

The present study has several limitations. Our study evaluated limited number of patients and follow-up period was only of one year. Therefore, our study results, especially the prognostic value of GLIM criteria compared to GNRI, should be interpreted cautiously and re-evaluated in the future large-scale study. Data on the prescription of some medications, including dietary supplementation, was not collected, and only oral medication taken at the time of discharge was recorded. Second, we evaluated the nutritional status only once before discharge, and no information was obtained regarding changes in nutritional status. Additional assessments of nutritional indexes during follow-up may provide useful information. It is also important to know whether dietary supplementation provides a survival benefit in patients malnourished, but this was not tested in the present study. Although intervention to malnutrition may have a large impact on clinical outcomes, it has been investigated in several small studies but few large, randomized trials. Further research is required to determine whether dietary supplementation can slow the progression of heart failure and reduce mortality among these patients in adequately powered randomized clinical trials. The present study was performed using a multicenter dataset, but it only included Japanese patients. This might be relevant as the average BMI is known to be lower in Asian populations compared to other populations; however, BMI and appendicular skeletal mass index cutoffs specific for Asian populations were proposed in the GLIM consensus report, which were applied to our cohort to take into account this issue. Nevertheless, confirmation of the present findings in different populations and diseases is needed. As volume status can change significantly, whether the cut-off for body weight reduction proposed for general population as a component for the diagnosis of malnutrition can be applicable to patients with heart failure is unknown. We supposed that the change in body weight occurs in a relatively short-term is reflecting changes in volume rather than nutritional status, and body weight changes observed over a longer period is more appropriately associated with patients' nutritional status. Moreover, relatively small body weight change can easily occur by the fluctuation of fluid status in patients with heart failure. We, therefore, used a higher threshold of >10% for 1 year, not >5% for 6 months, to identify body weight reduction more likely to be associated with nutritional status. Nevertheless, this point should be taken seriously as one of the limitations of our study.

5. Conclusion

The present study is the first to demonstrate the prevalence of malnutrition as defined by a set of proposed universal criteria, the GLIM criteria. We also evaluated the prognostic implications of malnutrition based on the GLIM criteria in elderly patients with heart failure, and showed that the GLIM criteria provide additive prognostic predictive ability. As malnutrition is one of the major fields in heart failure, but has been poorly investigated despite its strong association with prognosis, the clinically applicable GLIM criteria may facilitate research in this area, including the development of interventions to improve the nutritional status and (accordingly) the prognosis of patients with heart failure.

References

[1] Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003;22:235–9.
[2] Soderstrom L, Rosenblad A, Thors Adolfsson E, Bergkvist L. Malnutrition is associated with increased mortality in older adults regardless of the cause of death. Br J Nutr 2017;117:532–40.
[3] Wawrzenczyk A, Anaszewicz M, Wawrzenczyk A, Budzynski J. Clinical significance of nutritional status in patients with chronic heart failure-a systematic review. Heart Fail Rev 2019;24:671–700.
[4] Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr 2010;29:151–3.
[5] White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work G. Force ASPENMT and directors ASPENBo. Consensus statement: academy of nutrition and dietetics and American society for parenteral and enteral nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Parenter Enter Nutr 2012;36:275–83.
[6] Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - an ESPEN consensus statement. Clin Nutr 2015;34:335–40.
[7] Sargento L, Longo S, Lousada N, dos Reis RP. The importance of assessing nutritional status in elderly patients with heart failure. Curr Heart Fail Rep 2014;11:220–6.
[8] Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - a

consensus report from the global clinical nutrition community. Clin Nutr 2019;38:1—9.

[9] Matsue Y, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, et al. Prevalence and prognostic impact of the coexistence of multiple frailty domains in elderly patients with heart failure: the FRAGILE-HF cohort study. Eur J Heart Fail 2020;22:2112—9.

[10] Jensen GL, Cederholm T, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. J Parenter Enter Nutr 2019;43:32—40.

[11] Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. Br J Nutr 2004;92:799—808.

[12] Chen LK, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M, Asian Working Group for S. Recent advances in Sarcopenia research in asia: 2016 update from the asian working group for Sarcopenia. J Am Med Dir Assoc 2016;17:767 e1—7.

[13] Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005;82:777—83.

[14] Honda Y, Nagai T, Iwakami N, Sugano Y, Honda S, Okada A, et al. Usefulness of geriatric nutritional risk index for assessing nutritional status and its prognostic impact in patients aged >/=65 Years with acute heart failure. Am J Cardiol 2016;118:550—5.

[15] Kaneko H, Suzuki S, Goto M, Yuzawa Y, Arita T, Yagi N, et al. Geriatric nutritional risk index in hospitalized heart failure patients. Int J Cardiol 2015;181:213—5.

[16] Nishi I, Seo Y, Hamada-Harimura Y, Yamamoto M, Ishizu T, Sugano A, et al. Geriatric nutritional risk index predicts all-cause deaths in heart failure with preserved ejection fraction. ESC Heart Fail 2019;6:396—405.

[17] Sawano M, Shiraishi Y, Kohsaka S, Nagai T, Goda A, Mizuno A, et al. Performance of the MAGGIC heart failure risk score and its modification with the addition of discharge natriuretic peptides. ESC Heart Fail 2018;5:610—9.

[18] van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18:681—94.

[19] Barnard JRB. Small-sample degrees of freedom with multiple imputation. Biometrika 1999;86:948—55.

[20] Pencina MJ, D'Agostino RB, Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11—21.

[21] Lin H, Zhang H, Lin Z, Li X, Kong X, Sun G. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. Heart Fail Rev 2016;21:549—65.

[22] Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, et al. Prevalence and prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. JACC Heart Fail 2018;6:476—86.

[23] Fiorindi C, Luceri C, Dragoni G, Piemonte G, Scaringi S, Staderini F, et al. GLIM criteria for malnutrition in surgical ibd patients: a pilot study. Nutrients 2020;12.

[24] Yin L, Lin X, Li N, Zhang M, He X, Liu J, et al. Evaluation of the global leadership initiative on malnutrition criteria using different muscle mass indices for diagnosing malnutrition and predicting survival in lung cancer patients. J Parenter Enter Nutr 2020. https://doi.org/10.1002/jpen.1873.

[25] Einarsson S, Laurell G, Tiblom Ehrsson Y. Mapping the frequency of malnutrition in patients with head and neck cancer using the GLIM Criteria for the Diagnosis of Malnutrition. Clin Nutr ESPEN 2020;37:100—6.

[26] Uthamalingam S, Kandala J, Daley M, Patvardhan E, Capodilupo R, Moore SA, et al. Serum albumin and mortality in acutely decompensated heart failure. Am Heart J 2010;160:1149—55.

[27] Bonilla-Palomas JL, Gamez-Lopez AL, Moreno-Conde M, Lopez-Ibanez MC, Anguita-Sanchez M, Gallego de la Sacristana A, et al. Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. J Card Fail 2014;20:350—8.

[28] Matsue Y, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, et al. Clinical and prognostic values of ALBI score in patients with acute heart failure. Heart Lung Circ; 2019.