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Original article

The GLIM criteria for defining malnutrition can predict physical function and prognosis in cardiovascular disease

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SUMMARY

Background & aims: The Global Leadership Initiative on Malnutrition (GLIM) published a new international standard for defining malnutrition in 2018. Here, the GLIM criteria were compared with the European Society for Clinical Nutrition and Metabolism (ESPEN) criteria in relation to physical function and mortality risk in cardiovascular disease (CVD).

Methods: A total of 921 CVD patients ≥ 20 years old (67.8 ± 13.4 years, 631 men) hospitalised for heart failure (HF), acute coronary syndrome (ACS) and other conditions were stratified according to the presence or absence of malnutrition according to the GLIM and ESPEN criteria. Physical function was assessed by measuring grip strength, 6-minute walking distance (6MWD) and quadriceps isometric strength (QIS) before hospital discharge, and the endpoint was all-cause mortality.

Results: During the median follow-up period of 2.3 years (interquartile range [IQR], 0.9–3.5 years), 194 deaths occurred in the study population. Malnutrition defined by the GLIM criteria was significantly associated with low physical function. Malnutrition defined by both the GLIM and ESPEN criteria was significantly related to all-cause mortality ($P < 0.05$), and therefore could be used as predictors of mortality ($P < 0.05$).

Conclusions: Malnutrition defined according to the GLIM criteria was a predictor of low both physical function and mortality in CVD patients.

1. Introduction

Malnutrition is known to be associated with reduced levels of physical and immune function [1–3], reduced wound healing capacity [4] and prolonged hospital stays [5], and it has been shown to predict mortality [6]. Arteriosclerotic cardiovascular disease (CVD) has also been shown to result in reduced physical function and death [7,8].

At present, the European Society for Clinical Nutrition and Metabolism (ESPEN) criteria [9] are frequently used to identify malnutrition. However, the Global Leadership Initiative on Malnutrition (GLIM) published a new set of phenotypic criteria that included weight loss, low body mass index (BMI) and reduced muscle mass, as well as aetiological criteria, such as reduced food intake and inflammation, in September 2018 [10]. To date, however, the GLIM and ESPEN malnutrition criteria have not been compared with regard to physical function and mortality risk in CVD. Therefore, the present study was performed to compare the prognostic

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predictive capabilities of the GLIM and ESPEN criteria for malnutrition in patients with CVD.

2. Materials and methods

2.1. Study population

A retrospective review was performed in a cohort of 921 consecutive patients ≥20 years old with CVD, including heart failure (HF), acute coronary syndrome (ACS), aortic disease and others, admitted to the Cardiovascular Center of Kitasato University Hospital in whom nutritional evaluation with the GLIM and ESPEN criteria could be evaluated based on the electronic medical records between December 2011 and April 2016. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Kitasato University Hospital.

2.2. Data collection

The clinical details of presentation (medications, comorbidities) and demographic and biochemical data immediately before discharge were obtained from the electronic medical records. Height was measured to the nearest 0.1 cm using a stadiometer and weight was measured to the nearest 0.1 kg using a calibrated scale at the time of hospital discharge. BMI was then calculated as follows: BMI = body weight (kg)/height $(m)^2$.

The estimated glomerular filtration rate (eGFR) [11] was calculated using the Japanese Society of Nephrology formula: $194 \times (\text{serum creatinine})^{1.094} \times (\text{age})^{0.287}$ for men; $194 \times (\text{serum creatinine})^{1.094} \times (\text{age})^{0.287} \times 0.739$ for women.

The time to the endpoint (all-cause mortality) was calculated as the number of days from the date of measurements according to the GLIM and ESPEN criteria to the date of hospital discharge.

2.3. Physical function measurements

Several indicators of physical function were measured 3–7 days before hospital discharge. Handgrip strength was measured using a digital dynamometer (TKK 5101 Grip-D; Takei, Tokyo, Japan), with the patient sitting on a bench with the elbow joint flexed 90°. The subject squeezed gradually and continuously for 3 s with the right and left hands in turn, and the greatest strength values on the right and left sides were averaged and expressed as an absolute value (kg).

Maximum quadriceps isometric strength (QIS) was measured using a handheld dynamometer (μ-Tas; ANIMA, Tokyo, Japan) fixed to a rigid bar with the patient sitting on a bench. Data on the 5-s maximal isometric voluntary contraction of the quadriceps were collected three times successively for both legs with the knee joint angle fixed at 90° flexion. The right and left quadriceps were tested consecutively, with a rest period of 30 s between bilateral contractions. Telemetry was used for continuous monitoring of the electrocardiographic data, and the patients were instructed not to hold their breath during contractions to avoid the valsalva manoeuvre. The highest values on the right and left sides were averaged and expressed as both the absolute value (kg) and as a value relative to body weight (% BW). The 6-minute walking distance (6MWD) was determined by measuring the distance covered by the patient over 6 min with use of any necessary assistive devices, as outlined by the American Thoracic Society [12].

2.4. Nutritional assessment

The nutritional status of the patients before hospital discharge was evaluated according to the GLIM and ESPEN criteria for malnutrition (Table 1). Using the GLIM criteria, the first stage involved screening for risk of malnutrition using the geriatric nutritional risk index (GNRI) based on albumin level and BMI as indicated in Formula (1) below before hospital discharge with GNRI ≤ 98 taken to indicate malnutrition [10,13]:

$$\text{GNRI} = 14.89 \times \text{serum albumin}\,(\text{g}\cdot\text{dL}^{-1}) + 41.7 \times \text{body weight}\,(\text{kg})/[(\text{height})^2\,(\text{m})^2 \times 22] \quad (1)$$

The second step involved diagnosis of malnutrition based on the three phenotypic components [(i) nonvolitional weight loss > 5% within the past 6 months or > 10% beyond 6 months; (ii) BMI < 18.5 $\text{kg}\cdot\text{m}^{-2}$ for age < 70 years, < 20 $\text{kg}\cdot\text{m}^{-2}$ for age > 70 years; and (iii) low appendicular skeletal muscle mass index (ASMI) (males < 7.0 $\text{kg}\cdot\text{m}^{-2}$, females < 5.4 $\text{kg}\cdot\text{m}^{-2}$)] [14] and two aetiological components [(iv) reduced food intake < 50% of energy requirements > 1 week; and (v) inflammatory status such as COPD, cancer, HF and CKD. Malnutrition was diagnosed based on a combination of three phenotypic and two aetiological components, with at least one of each phenotypic and aetiological component necessary for a positive diagnosis according to the GLIM criteria.

ASMI was estimated using equation (2), which has previously been validated in Asian populations and was reported to have an adjusted R^2 of 0.90 with dual-energy X-ray absorptiometry (DEXA) as the gold standard.

$$\text{ASMI} = 0.193 \times \text{weight} + 0.107 \times \text{height} - 4.157 \times \text{gender} - 0.037 \times \text{age} - 2.631 \quad (2)$$

gender: 1 for men and 2 for women

Food intake was determined based on the electronic medical records evaluated subjectively by nurses who recorded the daily percentage of food intake.

The first stage of evaluation with the ESPEN criteria [9] again involved screening for malnutrition risk based on the GNRI before discharge calculated using Formula (1) above, with GNRI ≤ 98 taken to indicate malnutrition [13]. Patients classified as being at risk were then either diagnosed for malnutrition according to BMI <18.5 [9].

2.5. Statistical analysis

Continuous variables are expressed as the means ± standard deviation, while categorical variables are expressed as numbers and percentages. The patients were divided into two groups according to the GLIM and ESPEN criteria to investigate their effects on outcomes. Between-group comparisons of baseline characteristics and physical function were performed using the *t* test or Fisher's exact test as appropriate. Physical function outcomes, including low grip strength (<26 kg for men and <18 kg for women) [15], short 6MWD (<400 m) [16] and QIS (<40%BW) [17], were compared between groups by GLIM and ESPEN criteria using logistic regression analysis and linear regression analysis with adjustment for two models:

- Model 1: adjusted for age and sex
- Model 2: adjusted for factors in Model 1 + HF + ACS.

The adjusted odds ratios (OR) are reported with the corresponding 95% confidence intervals (95% CI). The cumulative

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Table 1
Criteria for nutritional assessment.

		Criteria
GLIM criteria [10]		
(i)	Nonvolitional weight loss	> 5% within past 6 months or > 10% beyond 6 months
(ii)	Low BMI	BMI < 18.5 kg·m^{-2} for age < 70 years, < 20 kg·m^{-2} for age > 70 years
(iii)	Reduced muscle mass	ASMI < 7.0 kg·m^{-2} for males, < 5.4 kg·m^{-2} for females
(iv)	Reduced food intake	< 50% of energy requirements > 1 week
(v)	Inflammatory conditions	Inflammatory disease (COPD, cancer, heart failure, CKD)
ESPEN criteria [9]		
The criteria for risk of malnutrition using a validated risk screening tool must be fulfilled before considering a diagnosis of malnutrition.		
• BMI < 18.5 kg·m^{-2}		

BMI, body mass index; ASMI, appendicular skeletal muscle mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

incidence of mortality during follow-up according to GLIM and ESPEN criteria was calculated by Kaplan–Meier analysis. Cox proportional hazards regression analysis was performed to evaluate the prognostic capabilities of GLIM and ESPEN criteria with the construction of two predictive models similar to linear regression analysis. The relationship between age and the prevalence of malnutrition was examined based on the *P* for trend with the Cochran-Armitage trend test.

Statistical analyses were performed using JMP® Pro 13.2 (SAS Institute Inc., Cary, NC). In all analyses, a two-tailed $P < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Patient characteristics

Table 2 shows the baseline characteristics for all subjects. The study population consisted of 921 CVD patients ≥20 years old (67.8 ± 13.4 years, 631 men) hospitalised for HF (45.9%), ACS (20.4%), aortic disease (9.1%) and other clinical entitles (2.6%). The patients were stratified into two groups with and without malnutrition according to the GLIM and ESPEN criteria, which identified malnutrition in 174 (18.9%) and 101 (11.0%) of the patients,

Table 2
Baseline characteristics.

Characteristics	Overall	GLIM			ESPEN		
	n = 921	With malnutrition *n* = 174	Without malnutrition *n* = 747	*P*-value	With malnutrition *n* = 101	Without Malnutrition *n* = 820	*P*- value
Age (years)	67.8 ± 13.4	74.4 ± 11.4	66.2 ± 13.3	<0.001	68.7 ± 14.9	67.8 ± 13.2	0.77
Male sex (%)	631 (68.5)	98 (46.9)	533 (74.9)	<0.001	45 (44.6)	586 (71.5)	< 0.001
Height (cm)	161.6 ± 9.3	156.4 ± 9.2	162.9 ± 9.0	<	157.7 ± 9.2	162.1 ± 9.2	< 0.001
Body weight (kg)	61.6 ± 14.3	45.8 ± 6.9	65.2 ± 13.1	<0.001	42.4 ± 6.3	63.9 ± 13.2	< 0.001
BMI (kg·m^{-2})	23.4 ± 4.4	19.0 ± 2.8	23.9 ± 3.8	<0.001	17.0 ± 1.4	24.2 ± 4.0	< 0.001
Dietary intake (%)	86.0 ± 25.0	73.5 ± 33.7	88.6 ± 22.0	<0.001	78.0 ± 30.3	87.0 ± 24.1	< 0.001
ASMI (kg·m^{-2})	7.56 ± 0.9	5.62 ± 1.0	7.31 ± 1.2	<0.001	6.29 ± 0.4	7.7 ± 0.8	< 0.001
Comorbidities							
Hypertension, *n* (%)	465 (50.5)	77 (41.4)	388 (51.9)	0.01	43 (42.6)	417 (50.9)	0.14
Dyslipidaemia, *n* (%)	460 (49.9)	59 (33.9)	401 (53.7)	< 0.001	25 (24.8)	435 (53.0)	< 0.001
Diabetes mellitus, *n* (%)	388 (42.1)	57 (32.8)	331 (44.3)	0.006	34 (33.7)	354 (43.2)	0.07
Diagnosis							
HF, *n* (%)	423 (45.9)	141 (81.0)	282 (37.8)	<0.001	57 (56.4)	366 (44.6)	0.03
ACS, *n* (%)	188 (20.4)	10 (5.8)	178 (23.8)	<.001	12 (11.9)	176 (21.5)	0.03
Aortic disease, *n* (%)	84 (9.1)	7 (4.0)	77 (10.3)	<0.001	8 (7.9)	76 (9.3)	0.85
Others, *n* (%)	24 (2.6)	1 (0.6)	23 (3.1)	0.07	3 (3.0)	21 (2.6)	0.74
Current smoker, *n* (%)	194 (21.1)	24 (14.4)	170 (23.3)	0.01	21 (20.8)	173 (21.0)	1.00
COPD, *n* (%)	57 (6.2)	27 (15.5)	30 (4.0)	<0.001	19 (18.8)	38 (4.6)	< 0.001
Cancer, *n* (%)	141 (15.3)	56 (32.2)	85 (11.4)	<0.001	30 (29.7)	111 (13.5)	< 0.001
CKD, *n* (%)	560 (60.8)	115 (66.1)	445 (59.6)	0.12	51 (50.5)	509 (62.1)	0.03
Prior HF, *n* (%)	222 (24.1)	68 (39.1)	154 (20.6)	<0.001	33 (32.7)	189 (23.0)	0.04
Laboratory data							
Creatinine (mg·dL^{-1})	1.4 ± 1.7	1.5 ± 1.6	1.4 ± 1.7	0.43	1.4 ± 1.8	1.5 ± 1.6	0.28
Albumin (g·dL^{-1})	3.6 ± 0.5	3.3 ± 0.5	3.7 ± 0.5	< 0.001	3.3 ± 0.5	3.6 ± 0.5	< 0.001
Total cholesterol (mg·dL^{-1})	167.9 ± 43.2	161.1 ± 41.2	169.2 ± 43.5	0.03	163.4 ± 40.7	168.2 ± 43.4	0.16
TLC (per μL)	1451.0 ± 652.2	1252.0 ± 603.0	1496.0 ± 654.9	< 0.001	1278.9 ± 675.0	1470.7 ± 646.6	0.003
eGFR (mL·min^{-1}·1.73 m^{-2})	53.6 ± 24.1	50.8 ± 29.8	24.3 ± 22.6	0.10	61.5 ± 34.0	52.7 ± 22.5	< 0.001
GNRI	97.1 ± 13.0	84.1 ± 9.4	100.1 ± 11.8	< 0.001	80.6 ± 10.0	99.1 ± 11.8	< 0.0001
Grip strength (*n* = 703), kg	25.4 ± 9.3	18.5 ± 7.3	26.7 ± 9.0	< 0.001	17.7 ± 6.7	26.3 ± 9.1	< 0.001
< Cut-off, *n*	303 (27.7)	83 (74.1)	220 (37.2)	< 0.001	52 (51.5)	251 (30.6)	< 0.001
6MWD (*n* = 629), m	410.1 ± 126.6	330.6 ± 128.0	424.7 ± 120.8	<0.001	362.7 ± 146.0	415.4 ± 123.3	0.002
< 400 m, *n*	255 (32.9)	64 (65.3)	191 (36.0)	<0.001	34 (33.7)	221 (27.0)	0.03
QIS (*n* = 711), %BW	43.7 ± 15.9	38.4 ± 14.2	44.7 ± 16.0	<0.001	39.8 ± 15.0	44.2 ± 16.0	0.01
< 40% BW, *n*	310 (33.7)	70 (63.1)	240 (40.0)	<0.001	42 (41.6)	268 (32.7)	0.005
All-cause mortality	194 (21.1)	66 (37.9)	128 (17.1)	<0.001	28 (27.7)	166 (20.2)	0.09

Values are means ± SD or *n* (%). Grip strength cut-off values: male <26.0 kg, female <18.0 kg.
BMI, body mass index; ASMI, appendicular skeletal muscle mass index; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HF, heart failure; TLC, total lymphocyte count; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; 6MWD, 6-minute walking distance; QIS, quadriceps isometric strength.

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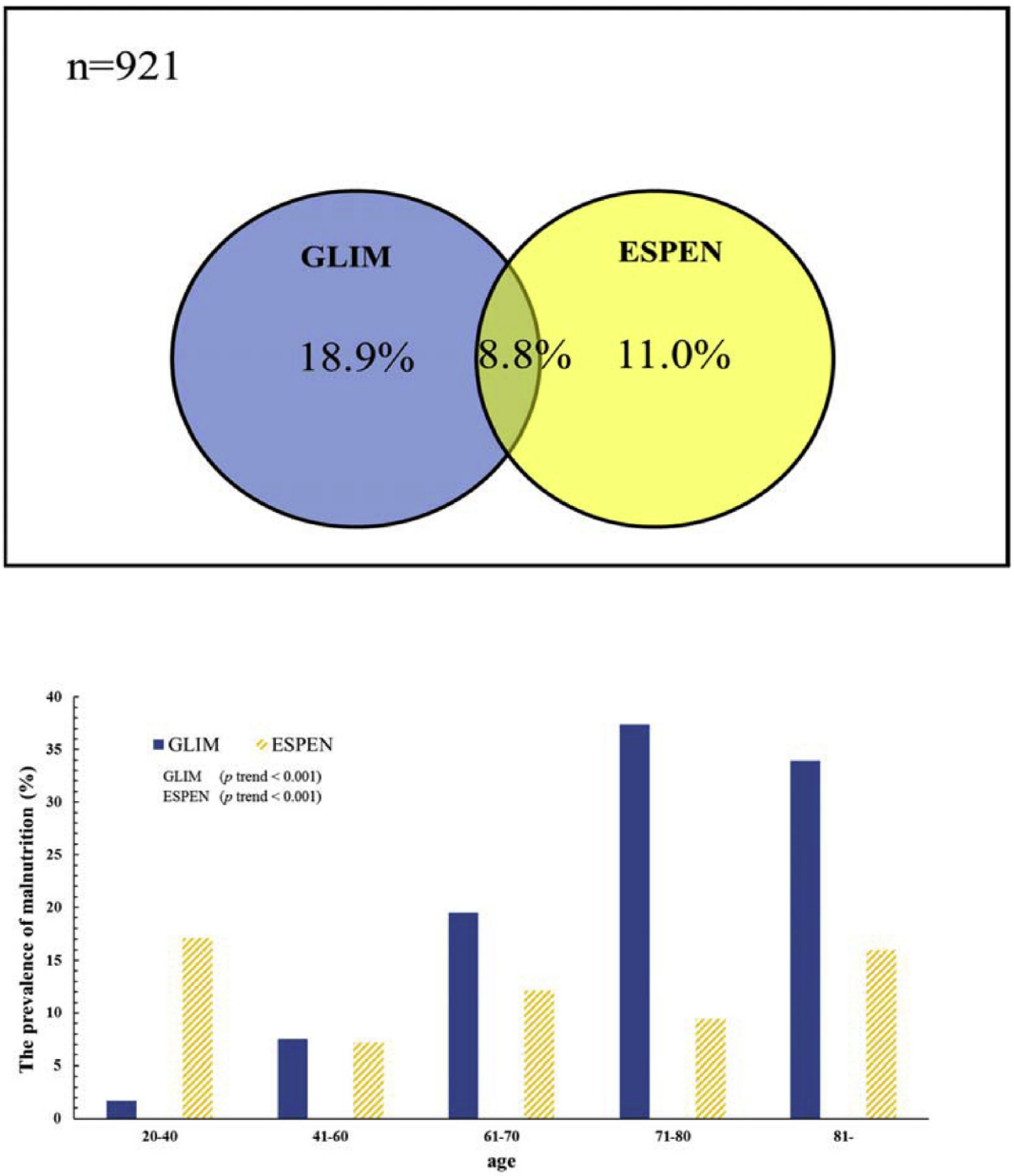

Fig. 1. Prevalence of malnutrition. GLIM, The Global Leadership Initiative on Malnutrition; ESPEN, The European Society for Clinical Nutrition and Metabolism. The relationship between age and the prevalence of malnutrition was examined using *P* for trend by the Cochran-Armitage trend test.

Table 3
Associations of GLIM and ESPEN malnutrition with clinical cut-off values.

Variable	Grip Strength < cut-off			6MWD <400 m			QIS <40%		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Unadjusted									
GLIM	5.73	3.70–8.88	<0.001	3.35	2.13–5.27	<0.001	2.56	1.68–3.89	<0.001
ESPEN	3.94	2.29–6.75	<0.001	1.76	1.05–2.96	0.03	2.09	1.26–3.45	0.004
Multivariate logistic regression									
Model 1									
GLIM	3.14	1.93–5.10	<0.001	1.82	1.09–3.06	0.02	1.46	0.92–2.32	0.10
ESPEN	3.66	2.02–6.62	<0.001	1.82	0.98–3.37	0.06	1.54	0.88–2.70	0.13
Model 2									
GLIM	2.77	1.68–4.58	<0.001	1.52	0.89–2.63	0.13	1.13	0.70–1.82	0.62
ESPEN	3.46	1.89–6.32	<0.001	1.80	0.94–3.50	0.08	1.43	0.81–2.51	0.21

Model 1, adjusted for age and sex; Model 2, adjusted for model 1 + heart failure and acute coronary syndrome.
OR, odds ratio; CI, confidence interval; 6MWD, 6-minute walking distance; QIS, quadriceps isometric strength. Grip strength cut-off values: male <26.0 kg, female <18.0 kg.

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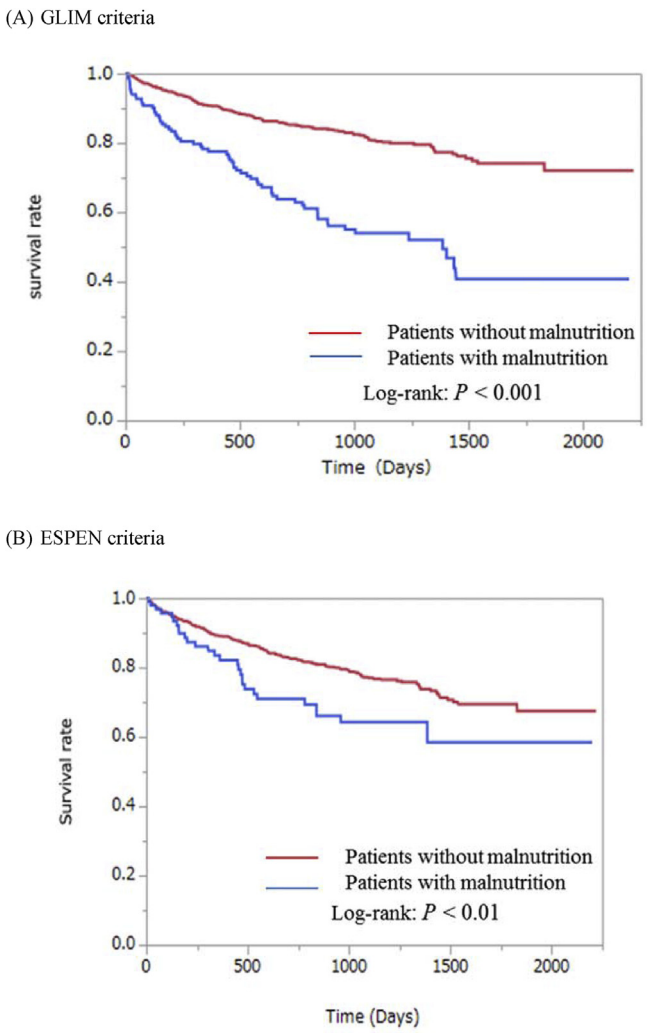

Fig. 2. Overall survival rates to (A) GLIM malnutrition and (B) ESPEN malnutrition. GLIM, The Global Leadership Initiative on Malnutrition; ESPEN, The European Society for Clinical Nutrition and Metabolism.

respectively (Fig. 1). The prevalence of malnutrition defined according to the GLIM criteria was high in patients over 60 years old (P for trend < 0.001).

3.2. Relationship between physical function and malnutrition

Univariate and multivariate logistic regression analyses were performed to determine the associations of malnutrition defined according to the GLIM and ESPEN criteria with low physical function (Table 3). Univariate analysis indicated that reduced physical function could be predicted by malnutrition defined according to both sets of criteria. After adjusting for age and sex, malnutrition defined according to the ESPEN criteria was significantly associated with a higher likelihood of having low hand grip strength. However, malnutrition defined according to the GLIM criteria remained a significant predictor of low physical function even after adjusting for age and sex with odds ratios of 3.14 for grip strength and 1.82 for 6MWD <400 m compared to the patients without malnutrition.

3.3. Association of malnutrition with all-cause mortality

There were 194 deaths in the study population over the follow-up period (median, 2.3 years; interquartile range [IQR], 0.9–3.5 years). Malnutrition defined according to the GLIM and ESPEN criteria showed significant associations with the endpoint of all-cause mortality on Kaplan–Meier survival curves (log-rank test, $P < 0.001$ and $P < 0.01$, respectively) (Fig. 2). The results of univariate and multivariate Cox proportional hazards regression analyses for all-cause mortality are shown in Table 4. On univariate analysis, malnutrition defined according to both the GLIM and ESPEN criteria significantly predicted mortality even after adjusting for age and sex (i.e., Model 1) and for age and sex + HF) + ACS (i.e., Model 2).

4. Discussion

Malnutrition defined according to the GLIM criteria was shown to be associated with low physical function, as indicated by reduced handgrip strength, 6MWD and QIS, and that defined according to both the GLIM and ESPEN criteria was associated with the endpoint of all-cause mortality in patients with CVD. To our knowledge, this is the first report that the GLIM criteria for malnutrition are useful for prediction of low physical function and mortality in patients with CVD.

The results of the present study indicated that the prevalence rates of malnutrition differed according to the criteria used (GLIM, 18.9% vs. ESPEN, 11.0%). Previous studies have reported malnutrition prevalence rates of 21.7% in community-dwelling people [18], 27% according to GNRI of 92–98 in rehabilitation care hospitalised patients > 65 years old [13] and 14% according to GNRI ≤ 98 in older patients with HF [19]. The reported prevalence rates of malnutrition defined according to the ESPEN criteria range from 19.3% [20] to 20.2% [21] in post-acute care patients > 70 years old, while Maeda et al. reported a prevalence rate of malnutrition defined according to the GLIM criteria of 18.0% among hospitalised patients ≥40 years of age, which varied between younger (<70 years old) and older (≥70 years old) subgroups (10.6% vs. 25.7%, respectively) [22].

Consistent with previous studies, our observations indicated that malnutrition defined according to the GLIM and ESPEN criteria was associated with mortality. The GLIM and ESPEN criteria for malnutrition both include BMI <18.5 kg·m^{-2}. A recent meta-analysis of 239 reports with data from 10,625,411 individuals, including East Asian subjects, showed that BMI <18.5 kg·m^{-2} is associated with increased mortality rate compared to BMI 18.5–20.0, 20.0–22.5 and 22.5–25.0 kg·m^{-2} [23].Taken together,

Table 4
Association of malnutrition with all-cause mortality.

Variable	Unadjusted			Adjusted by age + sex			Model 1 + HF and ACS		
	Univariate Cox proportional hazards regression analysis			Multivariate Cox Model 1			Multivariate Cox Model 2		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
GLIM	2.93	2.16–3.93	<0.001	2.66	1.93–3.62	<0.001	2.02	1.45–2.78	<0.001
ESPEN	1.66	1.09–2.43	0.02	1.90	1.24–2.82	0.004	1.71	1.11–2.53	0.02

HR, hazard ratio; HF, heart failure; ACS, acute coronary syndrome.

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these observations suggest that BMI is a strong prognostic factor in patients with malnutrition defined according to the GLIM and ESPEN criteria.

Malnutrition defined according to the GLIM and ESPEN criteria was shown to be associated with low physical function in the present study. To our knowledge, this is the first study to show that the GLIM and ESPEN criteria of malnutrition were useful for predicting low physical function in patients with CVD. Malnutrition has been shown to cause anabolic resistance, reduced blood flow, impaired regenerative capacity, mitochondrial dysfunction and insulin resistance, which can delay recovery from disease and increase mortality risk [24]. In addition, malnutrition has been shown to be a major risk factor of sarcopenia, defined as aging- and disease-related loss of muscle mass and function [25]. These findings and the results of the present study indicate the importance of routine nutritional assessment for CVD patients in clinical settings.

This study also had several limitations. First, this was a retrospective single-centre study in a CVD cohort consisting of patients hospitalized mainly for HF and ACS. In addition, we did not perform complex comprehensive nutritional assessments, such as monitoring of weight loss or free fat mass. Both ESPEN and GLIM recommend the Mini Nutritional Assessment (MNA) or Mini Nutritional Assessment-Short Form (MNA-SF) for identification of malnutrition. However, a previous study showed that the prognostic capability of GNRI was superior to MNA-SF in hospitalized elderly patients [26], and GNRI was also reported to show associations with all-cause mortality in Japanese patients undergoing haemodialysis [27] and CVD [28]. Moreover, associations of GNRI have also been reported with nutritional indicators, such as fat mass, lean body mass and arm circumference [29], as well as parameters of muscle function, such as grip strength, in elderly subjects [30]. Therefore, GNRI is considered to be useful for nutritional assessment. Finally, the study population consisted only of patients hospitalised with CVD, and therefore our findings may not be generalisable to other diseases or community-dwelling populations.

In conclusion, the results of the present study indicated that malnutrition defined according to the GLIM criteria is associated with low physical function and increased mortality risk in patients with CVD, and therefore the GLIM criteria are useful for predicting prognosis of patients with CVD.

Statement of authorship

YK, KK, NH and JA contributed to the conception or design of the work. YK, KK, NH, KN, TI, TN, MY, EM and MT contributed to the acquisition, analysis or interpretation of data for the work. YK and KK drafted the manuscript. NH, KN, TI, TN, MY, EM, MT, AM and JA critically revised the manuscript. All authors have given final approval and agree to be accountable for all aspects of work ensuring its integrity and accuracy.

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Conflicts of interest

The authors declare there are no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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