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Malnutrition Assessed by the GLIM Criteria Using 6 Different Approaches for Reduced Muscle Mass Criterion: Which Version Is Better Associated with Mortality in Community-Dwelling Older Adults?

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ABSTRACT

Objective: The Global Leadership Initiative on Malnutrition (GLIM) criteria suggest alternative methods for assessment of muscle mass, and which of these methods is more strongly associated with adverse outcomes remains an issue to be clarified. Our primary outcome was to report malnutrition prevalences defined by 6 different GLIM approaches and study their relationship with mortality.

Methods: This retrospective follow-up study included the data of outpatients admitted to a tertiary hospital. We used 6 different approaches for GLIM, based on methods used to identify reduced muscle mass: i) skeletal muscle mass (SMM)/height², ii) SMM/body mass index (BMI), iii) handgrip strength (HGS), iv) calf circumference (CC), v) CC adjusted for BMI, and vi) GLIM without third phenotypic criterion (P3). We evaluated survival in malnutrition with Kaplan–Meier log rank test. The Cox proportional hazards model was used to identify the relationships of different GLIM versions with mortality.

Results: The study population included 224 older individuals, with a median age of 72, and female predominance (68.8%). The prevalences with different GLIM versions ranged between 4.0% and 34.1%. During a median follow-up period of 31 months, 14 (6.3%) participants died. According to unadjusted analyses, only GLIM (SMM/h²), GLIM (HGS), GLIM (CC), and GLIM (without P3) were significantly associated with increased mortality risk [Hazard Ratio (95% CI) were 3.8 (1.1-13.7), 4.3 (1.4-12.8), 4.6 (1.3-16.7), and 7.3 (2.0-26.5), respectively]. After final adjustments were made for age and sex, it was revealed that none of the versions were the predictors of mortality in older outpatients.

Conclusion: The GLIM criteria have room for improvement as different options for muscle mass assessment are allowed, and this study aimed to fill the gap in the literature on whether malnutrition diagnosed by alternative GLIM definitions had predictive validity in community-dwelling older adults. Further outcome studies using larger cohorts and different pragmatic approaches are needed to detect the ideal GLIM definition for malnutrition assessment.

Keywords: Older adults, malnutrition, mortality, sarcopenia, survival

INTRODUCTION

Malnutrition is accepted as "a geriatric syndrome" that has significant relationships with adverse outcomes like sarcopenia, frailty, increased hospitalizations, and mortality.[1] The prevalence rates were primarily determined by settings, underlying diseases and methods used for assessment. A systematic review and meta-analysis using 22 different malnutrition screening tools have reported a pool prevalence of malnutrition in older adults ranging between 8.5% and 28.0% (for community-dwelling and hospitalized older adults, respectively), and the prevalence rates differed from 14.9% to 40.6%, depending on the method used for assessment of malnutrition.[2] Until 2019 (year of publication of the abovementioned systematic review and meta-analysis), there was a lack of consensus regarding the diagnostic criteria of malnutrition, leading to variations and inconsistencies between reports. Just in time, the Global Leadership Initiative on Malnutrition (GLIM) criteria were developed by the representatives of 4

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major clinical nutrition societies around the world with the aim of standardization of the clinical practice of malnutrition diagnosis.[3]

The GLIM criteria cover malnutrition diagnosis in quite a comprehensive way and require a 3-step approach: screening, diagnosis (searching for the presence of at least one phenotypic and one etiologic criterion), and grading of the severity. As a striking step, the panel implemented reduced muscle mass as one of the diagnostic criteria for malnutrition due to the close relationship between nutritional status and muscle health. Therefore, at the third phenotypic criterion, they recommended measurement of muscle mass with a validated tool, but proxy measurements were also welcomed in the absence of these tools.[3] A year after its publication, 2 of the main authors of the GLIM criteria assessed whether GLIM worked in older people and concluded that although predictive and criterion validity were acceptable, the lack of guidance on how to assess muscle mass hampered the validation and implementation of the GLIM criteria.[4] At the time of uncertainty on which diagnostic method is optimal for assessment of the third phenotypic criterion, it is assumed that further studies with different diagnostic tools will reveal the most useful version to properly detect malnutrition and predict adverse outcomes.

Another gap in the literature is that there are limited studies on GLIM-defined malnutrition and its outcomes in community-dwelling older adults, since the reports on GLIM-defined malnutrition have been mostly conducted on patients with specific diseases and different settings.[5-7] Therefore, the primary aim of this report is to find out the prevalence rates of GLIM-defined malnutrition with 6 different approaches in community-dwelling older adults and study the association of different GLIM definitions with mortality.

Main points

- The lack of guidance on how to assess the reduced muscle mass criterion of the Global Leadership Initiative on Malnutrition (GLIM) criteria hinders its validity and application in clinical practice. Therefore, studies with different diagnostic methods for the third phenotypic criterion are needed to identify the most useful version to properly detect malnutrition and predict adverse outcomes.
- The GLIM criteria with 6 different pragmatic approaches for reduced muscle mass criterion ended up with a broad range of malnutrition prevalence in older outpatients: The GLIM criteria without P3 criterion had the lowest (4.0%), and the GLIM with skeletal muscle mass adjusted for body mass index had the highest malnutrition prevalence (34.1%).
- In a study population of mostly overweight–obese older adults with a low mortality rate during 31-month follow-up, none of the GLIM versions were independently associated with mortality after adjusting for age and sex.

METHODS

Population and Setting

This study is a retrospective, longitudinal study conducted in a geriatric outpatient clinic of a tertiary health center between May 2018 and December 2021. We included community-dwelling older adults aged over 60 years who provided informal consent for participating in a comprehensive geriatric assessment (CGA). Exclusion criteria were i) moderate-to-severe dementia; ii) severe depression; iii) certain conditions that might prevent reliable muscle strength measurements (i.e., hand osteoarthritis, stroke, peripheral artery disease, etc.), bioelectrical impedance analysis (BIA) measurements (i.e., edematous state, metal implants, inability to stand on 2 feet, etc.), or calf circumference (CC) measurements (i.e., edematous state, amputation of lower extremities, etc.); iv) conditions other than dementia and depression that might prevent healthy communication (like severe hearing impairment); v) acute, unstable, or deteriorating clinical conditions that prevent CGA to be optimally performed; and vi) refusal to participate. We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement.[8] The local ethics committee of Istanbul University Istanbul Faculty of Medicine gave approval to the study on November 25, 2022 (approval number: 1399682/2022).

Sample Size Calculation

We performed a sample size calculation based on the reported GLIM-defined malnutrition prevalences:[9,10] Using a power of 80%, a CI of 95%, and an error probability of 10%, we determined a sample size of 184 participants. Anticipating a dropout rate of 10%, a sample size of 202 participants was considered sufficient for this study.

Measurements

Interview on Baseline Characteristics and Comprehensive Geriatric Assessment

We obtained the demographical and clinical characteristics of the participants. We recorded information about marital status, education level, tobacco and alcohol use, chronic diseases, and medications. Expert geriatricians performed CGA and questioned falls in the previous year, fear of falling, sleep disturbance, constipation, urinary and fecal incontinence, and chronic pain, with closed-ended questions. We assessed functionality via Katz Activities of Daily Living (ADL)[11] and Lawton Instrumental ADL (IADL) scales.[12] We screened for sarcopenia and frailty via SARC-F questionnaire and FRAIL scales, respectively.[13,14] The scores obtained from these 5-itemed questionnaires

were interpreted as: increased sarcopenia risk for SARC-F ≥4 points, frail for FRAIL ≥ 3, pre-frail for FRAIL = 1 or 2, and robust for FRAIL = 0.

Assessment of Nutritional Status with Different Versions of the GLIM Criteria

We assessed malnutrition via Mini-Nutritional Assessment—Short Form (MNA-SF) and the GLIM criteria. We classified a MNA-SF score of less than 12 as undernutrition and less than 8 as malnutrition.[15] The GLIM evaluates malnutrition by 3 phenotypic and 2 etiologic criteria and necessitates the presence of at least 1 phenotypic and 1 etiologic criterion for diagnosis step of malnutrition assessment. Phenotypic criteria are i) nonvolitional weight loss (>5% within past 6 months, or >10% beyond 6 months), ii) low body mass index (BMI) (<20 kg/m² if <70 years, or <22 kg/m² if >70 years), and iii) reduced muscle mass by validated body composition techniques. Etiologic criteria are i) reduced food intake or assimilation and ii) disease burden/inflammation.[3] Since this is a retrospective study, and GLIM criteria were not published during the earlier periods of the data collection, we derived the data on weight loss of some participants from the items of MNA-SF and FRAIL scale that question weight loss during the past 3 months and past year. Likewise, we derived the data on the first etiologic criterion by using the first item of the MNA-SF (i.e., Has food intake decreased over the past 3 months due to loss of appetite, chewing or swallowing difficulties, or digestive problems?[15]). Although we could not assess disease burden for the second etiologic criterion, diagnosis of acute or chronic inflammatory diseases, or a C-reactive protein level >5 mg/L at admission were considered positive for second etiologic criterion.

The GLIM panel recommended measurement of muscle mass primarily by dual-energy absorptiometry (DXA) or other validated techniques like BIA. Considering that these instruments are not readily available in most settings, they also optionalized the use of anthropometric measurements or measurements of muscle strength as proxies of muscle mass.[3] Since our primary goal was to compare different versions of GLIM determined by alternative methods for the third phenotypic criterion, we used 5 different definitions based on the modality used for measurement, i.e., i) reduced muscle mass [with the definition of skeletal muscle mass (SMM) adjusted for height square], ii) reduced muscle mass (with the definition of SMM adjusted for BMI), iii) reduced muscle strength [with measurement of handgrip strength (HGS)], iv) reduced CC, and v) reduced CC adjusted for BMI. We measured muscle mass via BIA and used 2 SMM indices: SMM/h² and SMM/BMI. We used SMM/h² definition, since it was the most commonly used way to define reduced muscle mass globally; however, this adjustment method has also been criticized that it could overlook reduced muscle mass in obese or overweight individuals and SMM/BMI would be a better adjustment technique in terms of finding cases and reported to have better association with adverse outcomes.[16] Therefore, we also defined reduced SMM by adjustments for BMI. We used Tanita-BC532 bioelectrical impedance analyzer, which demonstrated a strong correlation with magnetic resonance imaging measurements.[17] We obtained fat free mass values and multiplied them with 0.566 to transform them into SMM. We measured body weight and height with a standardized stadiometer to the nearest 0.1 kg and 0.1 cm. We calculated BMI as body weight (kg) divided by height square (meters). The cutoffs used for SMMI were population-specific thresholds obtained from total SMM measurements via BIA and determined by calculating mean minus 1 standard deviation of young and healthy reference population (which was recommended by experts of GLIM for determining thresholds for mild-to-moderate reduced muscle mass).[18] Hence, low SMM/h² thresholds were 10.1 and 8.2 kg/m²,[18] and low SMM/BMI thresholds were 1.189 and 0.954 kg/BMI,[19] for males and females, respectively.

For measurement of muscle strength, we used a Jamar hydraulic hand dynamometer, applying a standardized protocol.[20] We asked the participants to keep their elbows at 90° flexion and their wrists in a neutral position and to apply their maximum strength 3 times with both hands separately and with 30-second rest intervals. We accepted the maximum HGS measured as the muscle strength value and used the population and sex-specific thresholds to identify reduced HGS, i.e., <35 kg and <20 kg, for males and females, respectively.[21] We measured CC at the level of widest circumference of nondominant leg via a nonelastic tape while the participants were standing. We used the population and sex-specific thresholds for reduced CC, i.e., <33 cm and <32 cm, for males and females, respectively.[22] As CC is highly affected from subcutaneous fat tissue and an evident difference of CC between different BMI categories has been put forth, Gonzalez et al[24] have suggested adjusting CC measurements for different BMI categories, except for normal BMI range of 18.5-24.9 kg/m².[23] They have suggested a practical formula as adding 4 cm to the measured CC value in those with BMI <18.5 kg/m² or subtracting 3, 7, or 12 cm from the CC value in BMI categories of 25-29, 30-39, and ≥ 40 kg/m², respectively, from the CC measurement.[24] We applied the aforementioned formula to obtain adjusted CC values and used the population and sex-specific thresholds mentioned previously to identify reduced adjusted CC. Apart from these measurements, we decided to define an alternative GLIM definition as "GLIM without any measurement regarding muscle mass," and aimed to find out whether we could show a significant association between "GLIM without

third phenotypic criterion" and mortality. The rationale behind this approach was that the third phenotypic criterion being the rate-limiting step for most settings that do not have any equipment for measurements regarding muscle mass or its proxies. Thus, we wanted to check how the relationship between GLIM and mortality would be affected when the reduced muscle mass criterion was not used.

In summary, we used 6 alternative GLIM definitions to assess malnutrition:

1. GLIM with P3 defined as SMM adjusted for height square
2. GLIM with P3 defined as SMM adjusted for BMI
3. GLIM with P3 defined as reduced HGS
4. GLIM with P3 defined as reduced CC
5. GLIM with P3 defined as reduced CC adjusted for BMI
6. GLIM without P3

The abovementioned measurements were performed by a single qualified physiotherapist. All participants gave informed consent prior to assessments. Deaths were ascertained by a death certification search at the end of December 2021, using Death Notification System (DNS) of Republic of Türkiye Ministry of Health. The DNS is a national electronic software program used by physicians for mandatory reporting of in- or out-of-hospital deaths nationwide.

Statistical Analysis

We presented the categorical data as numbers and percentages. We investigated the normality of numerical variables by using visual (histograms and probability plots) and analytical methods. Accordingly, we presented normal distributed variables as mean ± standard deviation and skew distributed ones as median (minimum and maximum). We compared 2 independent groups with *t*-test or Mann–Whitney *U*-test, where necessary. We used chi-square test with Yates correction and Fisher's exact test when appropriate for categorical data. For comparison of more than 2 categorical variable groups, we used chi-square test. In order to find out the coherence between different GLIM versions, we studied the overall concordance rate and reported the Cohen's kappa coefficient (κ). The κ values between 0.81 and 1 were considered as perfect, 0.6-0.8 indicated strong, 0.4-0.6 indicated moderate, 0.20-0.4 indicated low, between 0 and 0.20 indicated very slight agreement, and less than 0 indicated disagreement. We evaluated survival in malnutrition defined by different GLIM versions with Kaplan–Meier log rank test. We defined follow-up duration as "the time (months) between date of death (for deceased participants) or December 2021 (for alive participants) and date of the first evaluation." We performed Cox regression analysis to find out whether malnutrition defined by different GLIM versions was independently associated with mortality. We primarily performed a crude analysis (without any adjustments for confounding factors) between mortality and malnutrition as defined by different GLIM versions. Furthermore, we defined different models to perform regression analyses adjusted for confounding variables, which were found to be significantly associated with mortality in univariate analyses. Before including confounding variables in the same regression models, we checked whether multicollinearity existed and confirmed that there was no such strong relationship that would cause multicollinearity. We derived hazard ratio (HR) and 95% CI and used alpha of less than 0.05 as the level of significance. We used the Statistical Package for the Social Sciences Statistics for Windows 21.0 program for statistical analyses.

RESULTS

There were 224 participants included in the study; 68.8% were female. The median age was 72 (60-96). The median number of chronic diseases was 3 (0-8) and regular medications was 5 (0-17). Hypertension was the most prevalent chronic disease (72.0%), followed by diabetes mellitus (35.5%) and dyslipidemia (21.5%). According to the CGA findings, more than half of the study population suffered chronic pain (53.6%), and nearly half of them had fear of falling (47.3%) and urinary incontinence (46.0%). According to MNA-SF, undernutrition (MNA-SF <12) prevalence was 22.5%, and malnutrition prevalence was 2.3%. The baseline characteristics and CGA findings of the study population are given in Table 1.

During a median follow-up period of 31 months, 14 (6.3%) participants died, with male participants demonstrating higher mortality rate than females (12.9% vs 3.2%, $P = .006$). The comparisons of each GLIM criteria between alive and deceased groups and the prevalences of malnutrition according to different GLIM versions can be found in Table 2. The prevalences with different GLIM versions ranged between 4.0% and 34.1%, as GLIM defined by SMM/BMI giving the highest and GLIM defined without P3 criterion giving the lowest prevalence. The prevalences of GLIM-defined malnutrition were significantly higher in deceased groups only when GLIM defined by HGS, CC, or without P3 criterion (*P*-values were .004, .048, and .018, respectively).

Among the different GLIM versions, the strongest agreement existed between GLIM defined by CC and GLIM defined without P3 criterion [$\kappa = 0.824$ (0.655-0.993); $P < .001$], followed by GLIM defined by CC and GLIM defined

Table 1. Baseline Characteristics of the Study Population

	Total (n = 224)	Female (n = 154)	Male (n = 70)	*P*
Age[#]	72 (60-96)	72 (60-96)	75 (61-93)	**.007**
Marital status				**.005**
Married	134 (59.8%)	81 (52.6%)	53 (75.7%)	
Single/divorced/widow	90 (40.2%)	73 (47.4%)	17 (24.3%)	
Education level				**.005**
Illiterate	63 (28.1%)	56 (36.4%)	7 (10.0%)	
Primary school	91 (40.7%)	57 (37.0%)	34 (48.5%)	
Secondary school	28 (12.5%)	18 (11.7%)	10 (14.3%)	
Post secondary education	42 (18.7%)	23 (14.9%)	19 (27.1%)	
Tobacco use	14 (6.3%)	10 (6.5%)	4 (5.7%)	**<.001**
Alcohol use	9 (4.0%)	3 (1.9%)	6 (8.6%)	**<.001**
Number of chronic diseases*	3 (0-8)	3 (1-8)	3 (0-7)	.411
Number of regular medications*	5 (0-17)	5 (0-17)	4 (0-14)	.060
Chronic diseases				
Hypertension	144 (72.0%)	103 (76.3%)	41 (63.1%)	**.051**
Diabetes mellitus	71 (35.5%)	47 (34.8%)	24 (36.9%)	.770
Dyslipidemia	43 (21.5%)	33 (24.4%)	10 (15.4%)	.144
Hypothyroidism	35 (17.5%)	32 (23.7%)	3 (4.6%)	**.001**
IHD	30 (15.0%)	16 (11.9%)	14 (21.5%)	.072
COPD	10 (5.0%)	6 (4.4%)	4 (6.2%)	.731
Comprehensive Geriatric Assessment				
Falls in the previous year	81 (36.3%)	54 (35.3%)	27 (38.6%)	.637
Fear of falling	105 (47.3%)	79 (52.0%)	26 (37.1%)	**.040**
Urinary incontinence	103 (46.0%)	86 (55.8%)	17 (24.3%)	**<.001**
Fecal incontinence	12 (5.4%)	11 (7.1%)	1 (1.4%)	.110
Chronic pain	120 (53.6%)	92 (59.7%)	28 (40.0%)	**.006**
Constipation	66 (30.0%)	45 (30.0%)	21 (30.0%)	1.0
Sleep disturbance	79 (33.3%)	59 (38.3%)	20 (28.6%)	.334
Undernutrition (MNA-SF < 12)	50 (22.5%)	34 (22.4%)	16 (22.9%)	.935
Malnutrition (MNA-SF < 8)	5 (2.3%)	3 (2.0%)	2 (2.9%)	.652
Frailty	38 (17.0%)	29 (19.0%)	9 (12.9%)	.261
ADL*	6 (0-8)	6 (1-6)	6 (0-6)	.268
IADL*	8 (0-8)	8 (0-8)	8 (0-8)	.708
SARC-F ≥ 4	44 (20.4%)	32 (21.5%)	12 (17.9%)	.547
Measurements				
Height (cm)*	156 (135-181)	152 (135-178)	166 (146-181)	**<.001**
Body weight (kg)*	72.2 (42.0-128.8)	71.0 (43.5-117.6)	74.3 (42.0-128.8)	.177
BMI (kg/m²)[#]	30.2 ± 5.3	31.3 ± 5.3	27.8 ± 4.6	**<.001**
Handgrip strength*	24 (6-50)	22 (10-44)	34 (6-50)	**<.001**
CC*	37 (29-47)	38 (31-47)	37 (29-45)	**.017**
Adjusted CC*	33 (24-40)	32 (24-40)	33 (25-37)	.392
Mortality rate	14 (6.3%)	5 (3.2%)	9 (12.9%)	**.006**

P < .05 are given in bold.

ADL, activities in daily living; BMI, body mass index; CC, calf circumference; COPD, chronic obstructive pulmonary disease; IADL, instrumental activities in daily living; IHD, ischemic heart disease; MNA-SF, Mini-Nutritional Assessment-Short Form; SARC-F, strength, assistance in walking, rise from a chair, limb stairs, and falls.

*Median.

[#]Mean ± standard deviation.

Table 2. Malnutrition Prevalence According to Different Versions of the GLIM Criteria and Comparisons Between Alive and Deceased Groups

	Total	Alive	Deceased	*P*
GLIM P1*	16 (7.1%)	12 (5.7%)	4 (28.6%)	**.011**
GLIM P2#	10 (4.5%)	7 (3.3%)	3 (21.4%)	**.018**
GLIM P3 (SMM/h²^	26 (11.6%)	23 (11.0%)	3 (21.4%)	.212
GLIM P3 (SMM/BMI)^	208 (92.9%)	195 (92.9%)	13 (92.9%)	1
GLIM P3 (HGS)^	80 (36.0%)	70 (33.7%)	10 (71.4%)	**.004**
GLIM P3 (CC)^	16 (7.2%)	13 (6.3%)	3 (21.4%)	.069
GLIM P3 (CC-adjusted) ^, ∫	83 (37.4%)	78 (37.5%)	5 (35.7%)	.894
GLIM E1√	17 (7.6%)	14 (6.7%)	3 (21.4%)	.078
GLIM E2◦	68 (33.2%)	62 (32.3%)	6 (46.2%)	.304
GLIM total (without P3 criterion)	9 (4.0%)	6 (2.9%)	3 (21.4%)	**.018**
GLIM total (with P3 defined with SMM adjusted for height square)	16 (7.2%)	13 (6.3%)	3 (21.4%)	.069
GLIM total (with P3 defined with SMM adjusted for BMI)	70 (34.1%)	64 (33.3%)	6 (46.2%)	.345
GLIM total (with P3 defined with reduced handgrip strength)	37 (17.2%)	31 (15.3%)	6 (46.2%)	**.004**
GLIM total (with P3 defined with reduced calf circumference)	14 (6.3%)	11 (5.3%)	3 (21.4%)	**.048**
GLIM total (with P3 defined with reduced adjusted calf circumference)	39 (18.1%)	36 (17.8%)	3 (23.1%)	.709

P < .05 are given in bold.
BMI, body mass index; CC, calf circumference; GLIM, Global Leadership Initiative on Malnutrition; h, height; HGS, handgrip strength; SMM, skeletal muscle mass.
*GLIM P1 (first phenotypic criterion): >5%within past 6 months, or 10% beyond 6 months.
#GLIM P2 (second phenotypic criterion): Low BMI (kg/m²): <20 if <70 years, or <22 if ≥70 years.
^GLIM P3 (third phenotypic criterion): Reduced muscle mass by validated body composition measuring techniques (SMM/h² thresholds were <10.1 kg/m² and <8.2 kg/m²; SMM/BMI thresholds were <1.189 kg/BMI and <0.954 kg/BMI; reduced handgrip strength thresholds were <35 kg and <20 kg; reduced calf circumference thresholds were <33 cm and <32 cm, for males and females, respectively).
∫Calf circumference was adjusted for body mass index. The adjusted CC was obtained by adding 4 cm to the measured CC value in those with BMI <18.5 kg/m² or subtracting 3, 7, or 12 cm from CC value in those with BMI 25-29, 30-39, ≥40 kg/m², respectively from the CC measure.
√GLIM E1 (first etiologic criterion): Reduced food intake or assimilation.
◦GLIM E2 (second etiologic criterion): Inflammation (acute disease/injury or chronic disease related).

by SMM/h² [κ = 0.786 (0.619- 0.953); *P* < .001], and GLIM defined by SMM/h² and GLIM defined without P3 criterion [κ = 0.756 (0.570-0.942); *P* < .001]. The findings of concordance analyses between different versions of GLIM are found in Table 3.

Mean survival time was significantly shorter in participants with malnutrition defined by GLIM (SMM/h²) (37.1 vs. 41.6 months; log rank, *P* = .027), GLIM (HGS) (38.8 vs. 40.0 months; log rank, *P* = .004), GLIM (CC) (36.5 vs. 41.6 months; log rank, *P* = .010), and GLIM (without P3 criterion) (34.6 vs. 41.6 months; log rank, *P* < .001) (Figure 1). We defined 4 models to identify which versions of GLIM defined malnutrition were independently associated with increased mortality. According to model 1 (crude analysis): GLIM (SMM/h²) [HR (95% CI) = 3.8 (1.1-13.7), *P* = .040], GLIM (HGS) [HR (95% CI) = 4.3 (1.4-12.8), *P* = .009], GLIM (CC) [HR (95% CI) = 4.6 (1.3-16.7), *P* = .019], and GLIM (without P3 criterion) [HR (95% CI) = 7.3 (2.0-26.5), *P* = .003] were significantly associated with mortality. In model 2 (adjusted for age), only GLIM (without P3 criterion) demonstrated persistence in relationship with mortality [HR (95% CI) = 4.0 (1.1-14.6), *P* = .039]. Adjustments made for sex (model 3) revealed that GLIM (HGS) [HR (95% CI) = 4.2 (1.4-12.5), *P* = .010] and GLIM (without P3 criterion) [HR (95% CI) = 5.9 (1.6-21.7), *P* = .007] were the only predictors of increased mortality risk. In model 4 (adjusted for age and sex), it was revealed that none of the GLIM versions were independently associated with mortality (Table 4, Supplementary Table 1).

Table 3. Concordance Between Alternative Versions of Global Leadership Initiative on Malnutrition Criteria Developed by Integrating Surrogates of Muscle Mass Measurement

	SMM/h²	SMM/BMI	HGS	CC	Adj. CC	Without P3
SMM/h²	1					
SMM/BMI	0.201 (0.089-0.313)	1				
HGS	0.431 (0.260-0.602)	0.530 (0.406-0.654)	1			
CC	**0.786** (0.619-0.953)	0.194 (0.086-0.302)	0.372 (0.200-0.545)	1		
Adj. CC	0.410 (0.243-0.577)	0.551 (0.431-0.671)	0.422 (0.265-0.578)	0.478 (0.313-0.643)	1	
Without P3	**0.756** (0.570-0.942)	0.125 (0.116-0.134)	0.334 (0.164-0.505)	**0.824** (0.655-0.993)	0.361 (0.194-0.528)	1

P < .001 for all, except *P* = .002. K values indicating strong agreement are given in bold.
Adj. CC, adjusted calf circumference; BMI, body mass index; CC, calf circumference; h, height; HGS, handgrip strength; P3, third phenotypic criterion; SMM, skeletal muscle mass.

DISCUSSION

In this study, we created different versions of the GLIM criteria determined by alternative definitions of third phenotypic criterion. Accordingly, we found out that there was a broad range of malnutrition prevalence according to different versions, with GLIM without P3 criterion had the lowest (4.0%) and GLIM (SMM/BMI) had the highest (34.1%). In crude analyses, GLIM without P3 criterion demonstrated the strongest relationship with mortality, followed by GLIM (CC) and GLIM (HGS). After adjustments made for age and sex, we found out that the relationship no longer persisted between GLIM-defined malnutrition and mortality.

According to the GLIM criteria, malnutrition prevalence in community-dwelling older adults was between 4.0%-34.1% in our study. This broad range of prevalence with different methods for third criterion is striking, as it shows that although several methods were optionalized for measurements regarding this criterion, results might be totally different from one another depending on the preferred method. In our country, GLIM-defined malnutrition prevalence in community-dwelling older adults was reported to be 24.5%-32.2% in previous studies by using BIA-derived reduced fat-free mass index (adjusted for h²)[10] or appendicular lean mass index (adjusted for h²)[9] for the third phenotypic criterion. The preference of different modalities for the third phenotypic criterion appears to be an important determinant of these reported prevalences.

In our study, malnutrition prevalence was lowest with GLIM without P3 criterion. Apart from the exclusion of reduced muscle mass factor, one of the main reasons behind this finding might be that our outpatient clinic had a significant number of healthy older adults attending to visit for follow-up of stable chronic diseases and for preventive medicine. The median number of chronic diseases was 3, which was lower than the number reported previously for older adults living in the community.[25,26] Additionally, the mean BMI of the study population was 30.2 kg/m², meaning most of the participants were overweight and even class I obese. In a study population consisted of mostly overweight individuals, a diagnostic tool using BMI, weight loss, and reduced food intake would be expected to detect low number of malnutrition cases. Contrarily, the Cox proportional hazards model revealed that when GLIM was used without the reduced muscle mass criterion, it demonstrated the highest mortality risk in crude analysis compared to the versions with third phenotypic criterion. Hence, although GLIM without P3 identified less individuals with malnutrition among the GLIM versions, it was also the strongest version that predicted increased mortality risk in seemingly healthier older adults living in the community. This finding might be useful in settings where equipment or qualified personnel do not exist for measurements for third phenotypic criterion to detect malnutrition cases with increased mortality risk. In community-dwelling older adults, GLIM without P3 was reported to be independently associated with mortality after adjustments made for age, sex, number of concomitant diseases, number of drugs, physical activity level, and cognitive status [HR (95% CI) = 3.1 (1.7-5.7)].[27] In fact, although settings were different or populations were more specific compared to ours (like mainly older outpatients with cancer who were actively receiving treatment for their diseases,[5] or hospitalized patients with hip fracture[6] or COVID-19[28]), there are other studies reporting that malnutrition defined by GLIM without P3 criterion had no significant relationship with increased mortality after adjustments for confounding variables.

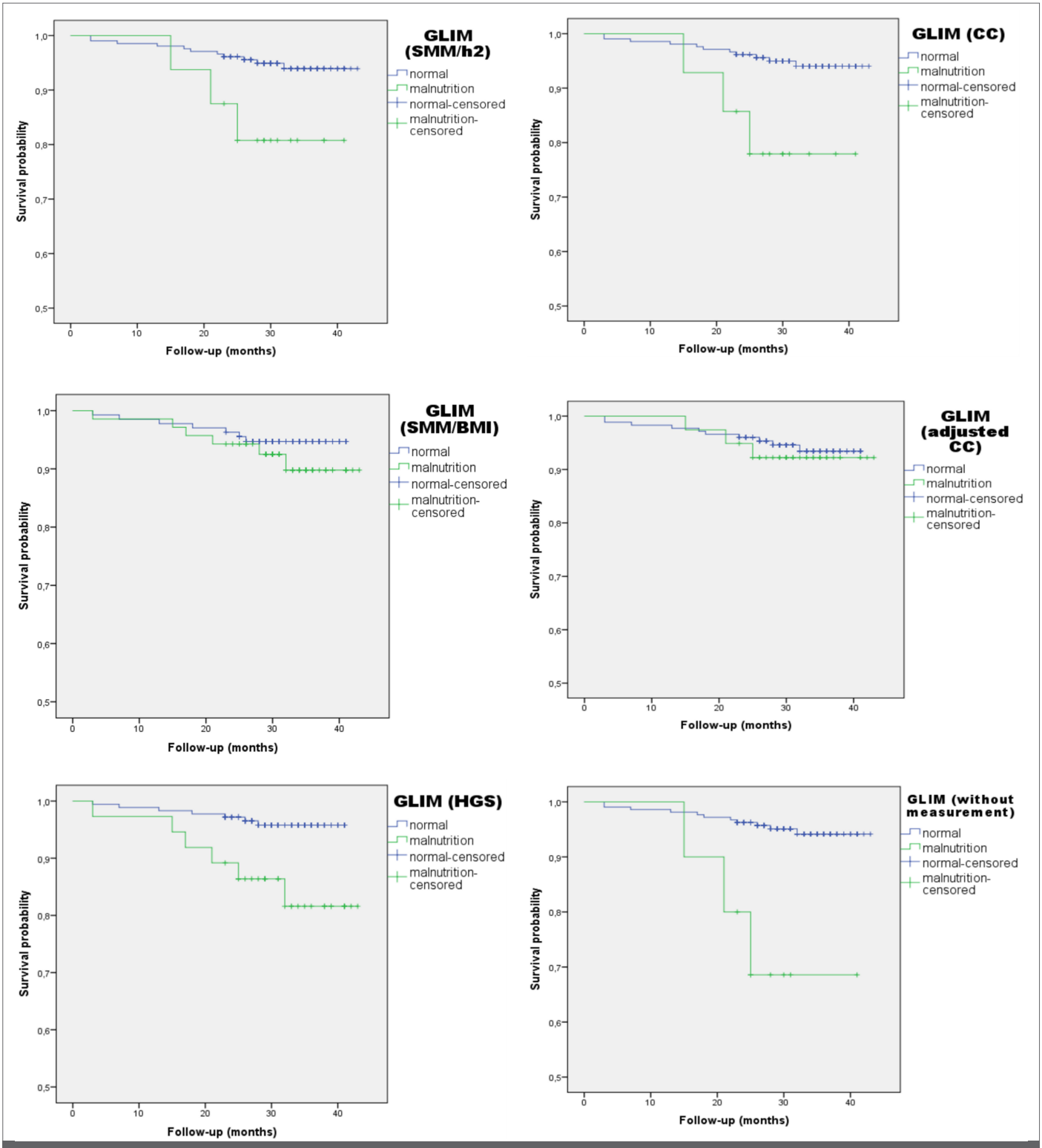

Figure 1. Kaplan–Meier survival curves with 6 different GLIM definitions for malnutrition diagnosis. BMI, body mass index; CC, calf circumference; GLIM, Global Leadership Initiative on Malnutrition; h, height; HGS, handgrip strength; P3, third phenotypic criterion; SMM, skeletal muscle mass.

Anthropometric measurements have been the most commonly used method for the third phenotypic criterion in previous studies with the GLIM criteria, and CC has been the most commonly used anthropometric measurement.[29] In our study, GLIM (CC) was the second version with the highest mortality risk in the unadjusted analysis, but the relationship did not persist in further models. Indeed, lower CC thresholds (which were

Table 4. Cox Regression Analyses Regarding Associations Between Malnutrition Defined by Different Versions of the GLIM Criteria and Mortality

Malnutrition Definition	Model 1	Model 2	Model 3	Model 4
GLIM (SMM/h²)	**3.8 (1.1-13.7)**	2.2 (0.6- 8.1)	2.3 (0.6-8.8)	1.5 (0.4-5.6)
	***P*=.040**	*P*=.221	*P*=.212	*P*=.594
GLIM (SMM/BMI)	1.7 (0.6-5.0)	1.1 (0.4-3.4)	1.9 (0.6-5.5)	1.2 (0.4-3.7)
	P=.363	*P* = .850	*P* = .272	*P* = .721
GLIM (HGS)	**4.3 (1.4-12.8**)	2.5 (0.9-7.6)	**4.2 (1.4-12.5)**	2.2 (0.7-6.9)
	***P* = .009**	*P* = .096	***P* = .010**	*P*=.174
GLIM (CC)	**4.6 (1.3-16.7**)	2.5 (0.7-9.2)	3.6 (0.98-13.0)	1.8 (0.5-6.9)
	***P* = .019**	*P* = .161	*P*=.054	*P*=.388
GLIM (adj. CC)	1.3 (0.4-4.9)	0.7 (0.2-2.6)	1.3 (0.4-4.6)	0.7 (0.2-2.7)
	P = .656	*P*=.566	*P* = .726	*P*=.619
GLIM (w/out P3)	**7.3 (2.0-26.5**)	**4.0 (1.1-14.6**)	**5.9 (1.6-21.7**)	3.0 (0.8-11.6)
	***P* = .003**	***P*=.039**	***P*=.007**	*P*=.117

Hazard ratios (95% confidence intervals) and p values with statistical significance are given in bold. Model 1 was the crude analysis performed with a single independent variable: Malnutrition defined by the GLIM criteria. Model 2 was adjusted for age; model 3 was adjusted for sex (female); model 4 was adjusted for age and sex (female). Age and sex were determined as confounding variables, as they were found to be significantly associated with mortality in univariate analyses.

adj. CC, adjusted calf circumference; BMI, body mass index; CC, calf circumference; GLIM, Global Leadership Initiative on Malnutrition; HGS, handgrip strength; P3, third phenotypic criterion; SMM, skeletal muscle mass.

suggested for the Turkish population as 31 and 30 cm for grading severe malnutrition in males and females, respectively[22]) would probably end up with stronger relationships in terms of mortality. Accordingly, we aimed to stratify the analyses for grading malnutrition, but unfortunately, we could not reach the exact data on weight loss questioned for the first phenotypic criterion. In the literature, 2 studies (1 with older patients with diabetes[30] and the other with older patients with cancer[31]) revealed that GLIM (CC)-defined malnutrition was independently associated with mortality for only severe, but not moderate, malnutrition after adjustments for confounding factors. We also used adjusted CC alternatively to exclude the confounding effect of BMI as an indicator of adiposity and identify if it would better predict mortality than unadjusted. Although this method identified more individuals with malnutrition, it demonstrated no significant relationship with mortality in any of the studied models. In fact, adjusting CC for BMI may have resulted in ignoring the interaction between muscle mass and fat mass and bypassing the negative (or may be positive) consequences of this close relationship. Furthermore, it might be necessary to come up with new thresholds for adjusted CC, as thresholds for unadjusted CC might not be applicable for the adjusted ones.

We used HGS for the P3 criterion alternatively and found that this definition was better associated with mortality than versions with muscle mass measurements. The GLIM (HGS) also identified more individuals with malnutrition compared to the GLIM (SMM/h²) (17.2% vs. 7.2%). In the literature, there are a plenty of studies reporting significant increase in mortality risk with reduced muscle mass criterion adjusted for height, based on either DXA or BIA measurements and conducted in different settings or study groups (patients with cancer,[32] heart failure,[7] or other cardiovascular diseases[33]). However, studies using HGS are less and more inconsistent. While in community-dwelling older adults, it was reported to be significantly associated with increased 5-year incidence of deaths,[27] it was not a predictor of mortality in older outpatients with heart failure[34] or cancer,[5] after adjustments made for confounding factors. It is obvious that more studies are needed to reveal whether GLIM (HGS) can be a strong alternative of reduced muscle mass measurement in community-dwelling older adults.

We also used BMI for SMM adjustments and defined another version for GLIM in order not to overlook the relative decrease in muscle mass in obese and overweight individuals.[35] Although GLIM-defined (SMM/BMI)

malnutrition was not an independent predictor of mortality, it identified more cases of malnutrition than any other GLIM version. Since our study population mostly consisted of overweight–obese individuals, SMM/BMI probably identified more individuals with reduced muscle mass in this group than other adjustment methods, hence ended up with more positivity on the third phenotypic criterion. The possible explanation for SMM/BMI not demonstrating a significant relationship with mortality might be "the obesity paradox," as being overweight or mildly obese has been reported to be protective in terms of mortality in older adults.[36] Likewise, several studies recently reported that obesity defined by fat percentage might also be protective in terms of mortality,[37] and when it accompanied to sarcopenia, it might be more favorable in terms of frailty, functionality, or physical performance than sarcopenia alone.[38,39] Hence, the study group may have benefited from the survival advantage of being overweight or mildly obese, even if they were malnourished according to GLIM (SMM/BMI). In fact, a lack of significant association with mortality does not mean that certain diagnostic method is not useful for routine practice, as detecting cases of malnutrition and timely intervention are expected to create significant impact on prognosis, even in obese older adults. As a matter of fact, this is the only study using SMM/BMI for third criterion of GLIM in the literature to the best of our knowledge, and more studies in different populations would reveal its exact relationship with mortality.

Although several methods were used for the third phenotypic criterion in GLIM, there are very limited studies that used more than one alternative in the same study for community-dwelling older adults. The most striking one was the SarcoPhAge study, as Sanchez-Rodriguez et al27 used 7 alternative approaches for the third phenotypic criterion (i.e., GLIM without P3, HGS, CC, mid-arm circumference, Yu's formula, Ishii's score chart, and Goodman grid), in addition to the original GLIM criteria (reduced muscle mass according to DXA-derived ALMI and FFMI). In a study population with 373 older adults, they reported a narrower range of prevalences for malnutrition, i.e., 13.9%-24.4%. Similar to our study, the lowest prevalence was obtained with GLIM without P3 criterion, and the highest was detected with the original GLIM criteria (i.e., reduced FFMI and ALMI). Different from our study, all the 8 approaches were independently associated with increased 5-year mortality risk despite confounding factors.[27] It is obvious from this conflicting result that more longitudinal studies from different populations with larger cohorts will determine which diagnostic method for third criterion is stronger to predict mortality and other adverse outcomes related to malnutrition.

This study harbors several limitations. First of all, it was conducted on outpatients living in the community who might be considered relatively healthier older adults. For reliable measurements, we had to exclude some of the most vulnerable individuals, such as patients with dementia or stroke, and this may have led to selection bias. Thus, the findings cannot be generalized to whole older adult population. Another limitation is the retrospective design of the study. Since GLIM criteria were not published during the commencement of the data collection, some items were indirectly assessed (like weight loss and reduced food intake and assimilation), and some might be assessed insufficiently (since disease burden was not assessed). In addition, although we reached out for information about mortality, we did not know the actual causes of deaths. Hence, the cause of mortality may have nothing to do with the nutritional status of the deceased individuals. Another major limitation can be considered as low mortality rate, since the relationship between malnutrition and mortality could have been stronger and more significant in a sample with a higher mortality rate. The major strength of the study is that it is one of the limited studies in the literature searching for the GLIM version that better predicted mortality among six different pragmatic approaches. Studies reporting the GLIM-mortality relationship are mostly conducted on populations with specific diseases (like cancer or surgery) and inpatients; therefore, we consider that a study searching for predictive validity of the GLIM criteria in outpatients with different comorbidity profiles will serve to fill the gap in the literature. Finally, we used the population-specific thresholds for all of the methods used to assess the third phenotypic criterion; hence, this represents a particular strength of the study that distinguishes it from many other similar studies that used nonspecific, conventional thresholds.

Our study revealed that the use of GLIM criteria in malnutrition practice among older outpatients living in the community resulted in a broad range of prevalences, depending on the definition used for the reduced muscle mass criterion. Moreover, none of the GLIM versions were independently associated with mortality, as increased age was the only significant predictor of mortality in an older population considered to be relatively healthy. The gap regarding the ideal GLIM version that both identifies malnutrition and predicts adverse outcomes better in this population will be filled with further longitudinal studies with larger cohorts and different approaches regarding the reduced muscle mass criterion.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul Faculty of Medicine (Date: November 25, 2022, Number: 1399682).

Informed Consent: Written informed consent was obtained from older adults who participated in this study.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Cox regression analyses showing association of different versions of GLIM and other independent factors with mortality

Independent variables	HR (95 % Confidence interval)	*P* value
GLIM (SMM/h²)		
Model 1		
GLIM (SMM/h²)	**3.8 (1.1 - 13.7)**	**0.040**
Model 2		
GLIM (SMM/h²)	2.2 (0.6 – 8.1)	0.221
Age	1.15 (1.1 – 1.2)	<0.001
Model 3		
GLIM (SMM/h²)	2.3 (0.6 – 8.8)	0.212
Sex (female)	0.3 (0.09 – 0.9)	0.028
Model 4		
GLIM (SMM/h²)	1.5 (0.4 – 5.6)	0.594
Age	1.15 (1.06 – 1.2)	<0.001
Sex (female)	0.4 (0.1 – 1.2)	0.088
GLIM (SMM/BMI)		
Model 1		
GLIM (SMM/BMI)	1.7 (0.6 – 5.0)	0.363
Model 2		
GLIM (SMM/BMI)	1.1 (0.4 – 3.4)	0.850
Age	1.15 (1.07 – 1.2)	<0.001
Model 3		
GLIM (SMM(BMI)	1.9 (0.6 – 5.5)	0.272
Sex (female)	0.3 (0.08 – 0.8)	0.022
Model 4		
GLIM (SMM/BMI)	1.2 (0.4 – 3.7)	0.721
Age	1.16 (1.06 – 1.2)	<0.001
Sex	0.4 (0.1 – 1.2)	0.095
GLIM (HGS)		
Model 1		
GLIM (HGS)	**4.3 (1.4 – 12.8)**	**0.009**
Model 2		
GLIM (HGS)	2.5 (0.9 – 7.6)	0.096
Age	1.15 (1.1 – 1.2)	<0.001
Model 3		
GLIM (HGS)	**4.2 (1.4 – 12.5)**	**0.010**
Sex (female)	0.3 (0.1 – 0.8)	0.021
Model 4		
GLIM (HGS)	2.2 (0.7 – 6.9)	0.174
Age	1.14 (1.05 – 1.2)	0.002
Sex (female)	0.4 (0.1 – 1.3)	0.138
GLIM (CC)		
Model 1		
GLIM (CC)	**4.6 (1.3 - 16.7)**	**0.019**
Model 2		
GLIM (CC)	2.5 (0.7 – 9.2)	0.161
Age	1.15 (1.1 – 1.2)	<0.001
Model 3		
GLIM (CC)	**3.6 (0.98 – 13.0)**	**0.054**
Sex (female)	0.3 (0.1 – 0.8)	0.019
Model 4		
GLIM (CC)	1.8 (0.5 – 6.9)	0.388
Age	1.15 (1.1 – 1.2)	<0.001
Sex (female)	0.4 (0.1 – 1.2)	0.095
GLIM (adj. CC)		
Model 1		
GLIM (adj CC)	1.3 (0.4 – 4.9)	0.656
Model 2		
GLIM (adj CC)	0.7 (0.2 – 2.6)	0.566
Age	1.16 (1.08 – 1.2)	<0.001
Model 3		
GLIM (adj CC)	1.3 (0.4 – 4.6)	0.726
Sex (female)	0.3 (0.1-0.8)	0.024
Model 4		
GLIM (adj CC)	0.7 (0.2 – 2.7)	0.619
Age	1.15 (1.07 – 1.3)	<0.001
Sex (female)	0.4 (0.1 – 1.2)	0.100
GLIM (without P3 criterion)		
Model 1		
GLIM (w/out P3)	**7.3 (2.0 – 26.5)**	**0.003**
Model 2		
GLIM (w/out P3)	**4.0 (1.1 – 14.6)**	**0.039**
Age	1.14 (1.1 – 1.2)	<0.001
Model 3		
GLIM (w/out P3)	**5.9 (1.6 – 21.7)**	**0.007**
Sex (female)	0.3 (0.1-0.9)	0.018
Model 4		
GLIM (w/out P3)	3.0 (0.8 – 11.6)	0.117
Age	1.13 (1.1 – 1.2)	0.001
Sex (female)	0.4 (0.1 – 1.2)	0.092

Abbreviations and acronyms: adj CC: adjusted calf circumference; BMI: body mass index; CC: calf circumference; GLIM: Global Leadership Initiative on Malnutrition; HGS: handgrip strength; HR: Hazard ratio; P3: third phenotypic criterion; SMM: skeletal muscle mass

*Model 1 is the unadjusted (crude) analysis between malnutrition defined by GLIM and mortality.

**Age and sex were identified as other independent variables in the Cox regression analyses in addition to malnutrition defined by the GLIM versions, as they were found to be significantly associated with mortality in univariate analyses.