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Original article

Prediction of 5-year mortality risk by malnutrition according to the GLIM format using seven pragmatic approaches to define the criterion of loss of muscle mass

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SUMMARY

Objectives: To assess the association between baseline malnutrition according to the GLIM format, using seven pragmatic approaches to define the criterion of loss of muscle mass, with mortality in the SarcoPhAge (*Sarco*penia and *Ph*ysical Impairment with advancing *Age*) study during a 5-year follow-up. Secondarily, to calculate diagnostic performance indicators, concordance, and feasibility of these 7 pragmatic approaches compared to the original GLIM criteria.

Methods: Post-hoc analysis of the SarcoPhAge cohort, which included 534 community-dwelling volunteers ≥65-year-old, followed-up from 2013 to 2019. Baseline malnutrition was defined by GLIM criteria and 7 approaches: 1) Omission of a reduced muscle mass as a criterion; 2) Substitution for handgrip strength, 3) Calf-circumference, 4) Mid-arm circumference, 5) Goodman's grid, 6) Ishii's score chart, and 7) Yu's formula. The association between malnutrition (according to GLIM criteria and the 7 approaches) and mortality was assessed by Cox-regressions. Sensitivity, Specificity, Positive (PPV), Negative (NPV) predictive values, area under the curve (AUC), Cohen−kappa coefficient, and TELOS-feasibility score were calculated.

Results: Data to calculate GLIM criteria were available for 373 subjects (73.07 ± 5.96 years, 56% women). Prevalence of malnutrition with GLIM criteria was 24.4% (ranged from 13.9% to 20.9% with the 7 approaches). GLIM criteria showed a HR = 3.38 (1.89−6.09) to predict mortality during the 5-year follow-up, which ranged from HR = 2.72 (1.51−4.91) to 3.94 (2.14−7.24) with the 7 approaches. All 7 approaches were feasible (TELOS ≥ 3), showed sensitivity ≥ 65%, specificity ≥ 95.4%, PPV ≥ 85%, NPV ≥ 88%, AUC ≥ 0.7 and had almost-perfect/strong concordance (k ≥ 0.7) with the original GLIM criteria.

Conclusions: GLIM criteria and the 7 approaches predicted three-to four-fold mortality, all ensured an accurate diagnosis, and were feasible in clinical settings.

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1. Introduction

Malnutrition is a major health concern in older people, is a strong predictor of the onset of sarcopenia [1,2], and is related to a reduced physical performance, poor outcomes during hospitalization, falls [3], and death [4–7]. One of the most remarkable features of malnutrition is that it can be reversed when early identified and targeted therapies are applied [2,8]. Despite an early adequate diagnosis being crucial for the comprehensive management of the disease, there had been no consensus on the definition of the disease until very recent times [9,10], malnutrition often remained underdiagnosed and undertreated, and it might cause an increase in mortality.

Aware of the burden of malnutrition, its negative impact in mortality, and the promising implications that a better

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List of abreviations

ALMI	Appendicular lean mass index
ASPEN	American Society for Parenteral and Enteral Nutrition
BIA	Bioimpedance analysis
DXA	dual energy X-ray assessment
SPEN	European Society of Clinical Nutrition and Metabolism
EuGMS	European Union Geriatric Medicine Society
EWGSOP2	Revised European consensus on definition and diagnosis
FFMI	Fat-free mass index
GLIM	Global Leadership Initiative on Malnutrition
IADL	Instrumental activities of daily living
ICD-10	International Classification of Disease
IGF-1	Insulin-growth factor 1
IL-6	Interleukin-6
MMSE	Mini-Mental State Examination
MNA	Mini-Nutritional Assessment
MRI	Magnetic resonance imaging
MSC score	Mental composite score
PSC score	Physical composite score
SarcoPhAge	*Sarco*penia and *Ph*ysical Impairment with advancing Age
SF	Short Form
SPPB	Short Physical Performance Battery

management of the disease might involve, the European Society of Clinical Nutrition and Metabolism (ESPEN), the Society of Sarcopenia, Cachexia, and Wasting Disorders (SSCWD), and the European Union Geriatric Medicine Society (EuGMS), among the largest international scientific societies of clinical nutrition and metabolism worldwide, boosted the Global Leadership Initiative on Malnutrition (GLIM) in 2016 [11]. Three remarkable goals were scheduled for the GLIM: First, developing an evidence- and consensus-based updated definition of malnutrition that incorporates the findings in research achieved in the last decades; second, to harmonize the new criteria and the International Classification of Disease (ICD-10). Finally, to implement the definition in clinical practice, as the overall goal is to improve quality of care in malnourished patients [8,10].

The first landmark has just been achieved: GLIM has launched a consensus-based definition of malnutrition formed by those phenotypic and etiologic criteria which have been shown to better capture the state of malnutrition. Meeting malnutrition according to the GLIM criteria requires at least one phenotypic [unintentional weight loss, low body mass index (BMI), or reduced muscle mass] AND at least one etiologic criterion (reduced food intake or assimilation and disease burden or inflammatory conditions) [10].

Muscle mass became part of the GLIM criteria because muscle structure and function depend on nutrition due to the balance between protein synthesis and degradation [12] and because it has been shown to be an independent factor of mortality [13,14]. Magnetic resonance imaging (MRI), dual energy x-ray assessment (DXA), and bioimpedance analysis (BIA) provide moderate to high quality data about muscle structure and are the recommended techniques to measure muscle mass [9,10,14]. However, these techniques are not standardized yet, have limited access for research, and are not feasible in most of healthcare settings [15,16] [17]. Aware of the challenge that the measurement of muscle mass involves for the widespread use of the GLIM criteria, GLIM proposed pragmatic approaches: Substituting a phenotypic criterion like calf-circumference or mid-arm circumference, or handgrip strength for muscle mass [10].

Muscle mass is also a component of sarcopenia as defined by the latest consensus published by the European Working Group on Sarcopenia in Older People (EWGSOP), the revised European consensus on definition and diagnosis (EWGSOP2) [14]. By sharing muscle mass, the new definitions of malnutrition and sarcopenia were harmonized, in order to gain knowledge and develop shared diagnostic and therapeutic interventions that might benefit the two diseases [18]. Some screening methods for sarcopenia have shown good correlation with muscle mass [19]: e.g. Ishii's score chart [20], Yu's formula [21], and Goodman's grid [22], and the equipment required to administer them (measuring tape, weighbridge, or handgrip dynamometer) is inexpensive, available in less resourced healthcare settings.

The capacity of the GLIM criteria to predict mortality has been recently shown in hospitalized patients with cancer [23] and in older patients with diabetes mellitus [24]; however, the capability of the GLIM criteria to predict mortality in community-dwelling older population remains unexplored. Moreover, the impact of the presence or the omission of muscle mass as part of the definition is still unknown and there are no data about the performance indicators of any pragmatic approach compared with the original GLIM criteria. Our hypotheses are that malnutrition according to the GLIM criteria and these 7 approaches (omission of a reduced muscle mass as a phenotypic criterion, or using as substitute for muscle mass handgrip strength, calf-circumference, mid-arm circumference, Goodman's grid, Ishii's score chart, or Yu's formula) assessed at baseline will be capable to predict mortality in general older population during a 5-year follow-up. Moreover, these 7 approaches might show good performance indicators and be more feasible. Therefore, their use might bridge this gap between research and clinical practice [25].

Objectives: Our primary objective was to calculate the association between baseline malnutrition according to the GLIM and the 7 pragmatic approaches, with the risk of mortality in community-dwelling older adults from the SarcoPhAge (*Sarco*penia and *Ph*ysical Impairment with advancing Age) study during a 5-year follow-up. Secondarily, we assessed the prevalence, diagnostic performance indicators, and concordance of the 7 pragmatic approaches, compared to the original GLIM criteria. Finally, we explored the feasibility of the GLIM criteria and the 7 approaches in clinical practice.

2. Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed [26].

2.1. Population

Post-hoc analysis of a cohort study, the SarcoPhAge study, which aimed on assessing health and functional adverse consequences of sarcopenia in community-dwelling older adults during a 5 years follow-up. The study was conducted in Belgium and included 534 older volunteers at baseline, which were annually followed-up from June 2013 to September 2019. A complete protocol of the SarcoPhAge study is available [1,27,28].

Inclusion criteria: Community-dwelling volunteers ≥65 years old were included in the SarcoPhAge cohort, with no selection criteria related to health or demographic characteristics. **Exclusion**

criteria: Amputated limb or body mass index (BMI) ≥50 kg/m^2. For this post-hoc analysis in the SarcoPhAge cohort, two additional eligibility criteria were applied: to have the variables needed to calculate the GLIM criteria available at baseline and the data of death available during the 5-year follow-up. Data collection and procedures have been previously described in detail [1,28,29].

2.2. Diagnosis of malnutrition according to GLIM criteria

Malnutrition according to the GLIM criteria is composed by a 3-step diagnostic structure [10]: screening, diagnosis, and severity grading. For the purpose of analysis, diagnosis of malnutrition was applied to all study sample at baseline and considered as a dichotomous variable (yes/no). Therefore, the first screening step and the severity grading step proposed by the GLIM were not applied in the study. The rationale for this decision was 1) because we wanted to include the largest number as possible of participants in the analyses; and 2) because the assessment, at baseline, of body composition and muscle mass by DXA was available in the whole study sample of the SarcoPhAge study.

Diagnosis of malnutrition according to the GLIM criteria requires at least one phenotypic criterion AND at least one etiologic criterion.

Phenotypic criteria

Weight loss (%): Body weight was measured in kilograms (kg) to the nearest 0.1 kg by a precision weighbridge. Clinical interview was used to obtain unintentional weight loss at baseline. Volunteers with an unintentional weight loss >4.5 kg in the past year were considered meeting this phenotypic criterion [30].

Low BMI (kg/m^2): Height was measured in meters (m). BMI (kg/m^2) was calculated and considered reduced if < 20 kg/m^2 in <70-year-old individuals and <22 kg/m^2 in ≥70-year-old [10].

Reduced muscle mass: The sum of muscle mass (fat-free mass) and muscle mass of the four limbs (appendicular lean mass) was determined by daily calibrated DXA (Hologic Discovery A, USA). Fat-free mass and appendicular lean mass (ALM) were divided by squared height to obtain fat-free mass index (FFMI) and appendicular lean mass index (ALMI) values (kg/m^2), respectively. Muscle mass was considered reduced in presence of either low FFMI or low ALMI, by using the sex-related thresholds: FFMI <17 in men and <15 kg/m^2 in women or ALMI <7 kg/m^2 in men and <5.5 kg/m^2 in women, following recommendations from the GLIM [10] and the EWGSOP2 [14].

Etiologic criteria

Reduced food intake or assimilation: Food intake was explored by the first item of the MNA-Short Form [31]: "Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?" Both severe and moderate decrease were considered as a positive answer [31]. Chronic gastrointestinal conditions that produced a negative impact in the absorption of nutrients or food assimilation were also considered.

Disease burden and inflammation: Insulin-like growth factor 1 (IGF-1) and interleukin-6 (IL-6) were used as blood-based biomarkers of inflammation, following recommendations by the Targeting Aging Biomarkers Workgroup [1,32]. Quartiles for IGF-1 and IL-6 were calculated for both sexes in our own sample and the lowest sex-specific quartile was considered as threshold: IGF-1: ≤88 ng/mL in men and ≤82 ng/mL in women and IL-6 >3.84 pg/mL in men and >2.99 pg/mL in women. Similar thresholds have been previously reported for community-dwelling older people [33,34]. Disease burden was not assessed; number of concomitant diseases was recorded. Blood samples were collected at baseline and analysed in standardized conditions. Data collection and procedures have been previously described in detail [1](28).

2.3. Malnutrition according to the 7 pragmatic approaches was calculated at baseline, as follows

2.3.1. GLIM criteria without a reduced muscle mass

Omission of a reduced muscle mass as a phenotypic criterion within the definition, which means only taking into account weight loss or low body mass index as phenotypic criterion.

Substitution of a reduced muscle mass as a phenotypic criterion within the definition for the following measurements:

2.3.2. GLIM criteria with calf circumference

Assessed (cm) with a measuring tape on the dominant side (e.g., right leg in right-handed individuals) in individuals in sitting position with feet plant resting on the floor, 90º-knee flexion at the point of bigger circumference without pressing the tissue. The <31 cm threshold for calf circumference was used [35–37].

2.3.3. GLIM criteria with handgrip strength

Measured (kg) by a yearly calibrated handgrip hand-held dynamometer (Saehan Corporation, MSD Europe Bvba, Belgium). Handgrip dynamometry was administered following standardized procedures: individuals in sitting position were encouraged to squeeze the hand-held dynamometer as hard as possible three times per hand. The highest value of the six measurements was selected for the analyses (Southampton protocol) [38]. Sex-specific thresholds for low muscle strength were <27 kg in men and <16 kg in women as recommended by the EWGSOP2 [14] and endorsed by ESCEO [39].

2.4. GLIM criteria with Ishii's score chart

The Ishii's score chart requires the measurement of calf-circumference and handgrip strength. The sex-specific scores were calculated as follows [20]: score in men, 0.62 × (age − 64) − 3.09 × (handgrip strength − 50) − 4.64 × (calf-circumference − 42); score in women, 0.80 × (age − 64) − 5.09 × (handgrip strength − 34) − 3.28 × (calf-circumference − 42). Sex-specific thresholds used were ≥105 for men and ≥120 for women [19,20].

2.5. GLIM criteria with mid-arm circumference

Assessed (cm) with a measuring tape on the dominant side (e.g., right arm in right-handed individuals) in individuals in sitting position with lower arm resting on a plain surface, 90º-elbow flexion at the point of bigger circumference without pressing the tissue, as recommended by the Report of the WHO Expert Committee for the use of and interpretation of anthropometry in older people [35] and reported by Frisancho et al., [40]. The lowest quartile (a value < 21 cm) was computed for SarcoPhAge and used as threshold [24].

2.6. GLIM criteria with Yu's formula

It requires the measurement of weight and height, and BMI. The appendicular skeletal muscle mass prediction equation was: 10.05 + 0.35 (weight) - 0.62 (BMI)-0.02 (age) +5.10 (if male). A value below the 20th percentile was computed for SarcoPhAge and used as threshold [19].

2.7. GLIM criteria with goodman grid [22]

Goodman grids provides the probability (%) of low muscle mass. It is constructed separately for men and women by using age and sex-specific BMI. A threshold ≥70% in men and ≥80% in women was considered as indicative of low muscle mass [22], as previously reported in SarcoPhAge [19].

2.8. Main outcome measure

Deaths during the 5-year follow-up in the SarcoPhAge study according to the presence of malnutrition at baseline. Data for the survival curve were collected annually by direct interview or assessed by medical records or phone calls with relatives and caregivers if the participant did not attend the annual visit. **Secondary outcome measures were:** 1) Diagnostic performance indicators [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC)], and concordance (Cohen–kappa coefficient) of the 7 pragmatic approaches of GLIM criteria compared to the original GLIM criteria. 2) Feasibility of the GLIM criteria and the 7 pragmatic approaches, measured by the Technological, Economical, Legal, Operational, Schedule (TELOS)-feasibility score.

Feasibility was defined as "the state or degree of being easily or conveniently done [41]" and explored by the TELOS-feasibility score, which assess the potential of implementation of new systems. This model is used in Engineering and has been also applied into Medicine [42]. Five areas were assessed by polar answers (yes/no): Technological ("Is the tool available in the clinical setting? Is staff trained to implement the new method?" Yes, if a training infrastructure is available in the clinical setting), Economic ("Is the cost of training acceptable? Is the training period less than 1 h?" Yes, if no additional cost in terms of money are needed, and less than 1 h of training period in terms of time), Legal ("Does the assessment conflict with legal requirements?"), Operational ("Does the assessment method solve a clinical problem? Is muscle assessment required in clinical practice?" Yes, if assessment of malnutrition is considered as relevant in clinical practice), and Schedule ("Does the procedure take less time than the current standard method of measurement?" Yes, if the procedure takes less than the time needed to measure muscle mass by the GLIM criteria). A positive answer scores 1 point in the TELOS-feasibility score, the legal area is not included in the sum up of the score, and a "no" in that area is mandatory to continue the study. Interventions were considered feasible if the TELOS-feasibility score was ≥3) [42]. The 5 questions were answered by the researchers on the basis of the data from two surveys about assessment of malnutrition [43] and sarcopenia [17] in clinical practice across European countries.

2.9. Covariate data collection

Clinical and demographic data were collected during annual interviews and phone calls and were used as covariates. Number of concomitant diseases and drugs taken were recorded. The Mini-Nutritional State Examination (MMSE) (maximum score 30 points) was used to assess cognitive status [44]. Instrumental activities of daily living (IADL) (maximum score 8 points) were assessed [45]. Sarcopenia was defined according to the EWGSOP2, by a low grip strength and low muscle mass. If low physical performance was also present, it was considered "severe sarcopenia" [14]. Sarcopenia was measured as recommended by the EWGSOP2 [14] and ESCEO [39] (see above). Diagnosis of sarcopenia was considered as a dichotomous variable (yes/no) and severity grading of sarcopenia was not assessed in our study for purpose of analysis, i.e., individuals with sarcopenia or severe sarcopenia computed equally. The Minnesota Leisure Time Activity Questionnaire was used to quantify the self-reported time spent in different physical activities in the past last 7 days and its sex-specific thresholds were followed [46]. The Short-form (SF) 36 Physical Component Summary (PCS) score, the SF-36 Mental Health Component Summary (MCS) score (maximum 100 points) [47], and the EuroQol 5D [(ranged from 0 (the worst possible health status) to 1 (the best possible health status)] [48] were administered at baseline to assess quality of life.

2.10. Statistical method

Absolute and relative (%) frequencies were used to express qualitative variables; mean ± standard deviation was used to express quantitative variables following a Gaussian distribution; median (percentile 25 – percentile 75) were used to express quantitative variables following a skewed distribution. The normality of the variables was checked by exploring the difference between the mean and the median values, the histogram, the quantile–quantile plot, and the Shapiro–Wilk test.

The characteristics of all subjects were evaluated at baseline. The number of participants with malnutrition diagnosed according to either GLIM criteria or the 7 pragmatic approaches were measured. Characteristics of subjects diagnosed with malnutrition with either GLIM criteria or the 7 pragmatic approaches were compared against subjects with no malnutrition through a logistic regression. Sex was introduced as a covariate in the regression for well-known sex-specific variables (muscle strength, fat-free mass, FFMI, ALMI, and gait speed).

The relationship between malnutrition and risk of mortality was explored. The Cox proportional hazards model, giving the hazard ratio (HR) and 95% confidence interval (CI) was applied for mortality. Crude and adjusted HR were computed for two models: in the first multivariate model, age and sex were included as confounders; in the second model, the age, sex, number of concomitant diseases, number of drugs, physical activity level and cognitive status were included as confounders, due to the known effect of these variables in muscle mass.

The performance indicators that determine the diagnostic properties of an assessment method were calculated for the GLIM criteria and the 7 pragmatic approaches: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC). An assessment method was considered to have good performance indicators if sensitivity and specificity>80%; fair, if sensitivity or specificity<80% but both values > 50%; and poor, if sensitivity or specificity<50% [49–51]. Coherence between GLIM criteria and the 7 pragmatic approaches was reported with the Cohen–kappa coefficient (overall concordance rate). Cohen-kappa (k) values between 0.81 and 1 were considered indicative of almost perfect agreement, 0.6–0.8 indicates strong agreement, 0.4–0.6 indicates moderate agreement, 0.20 to 0.4 indicates low agreement, between 0 and 0.20 indicates very slight agreement and less than 0, indicates disagreement [49,52]. The 5% critical level was considered as statistically significant. SPSS Statistics 24 (IBM Corporation, Armonk, NY, USA) software package was used for data analysis.

2.11. Ethical statements

National and international research ethics guidelines were followed [53], including the Deontological Code of Ethics, 1964 Declaration of Helsinki and its later amendments. Data were entered and treated in accordance with the provisions of the applicable data protection law in Belgium and the General Data

Protection Regulation (GDPR) (EU) nº 2016/679 of the European Parliament and Council, dated the 27 April of 2016, which entered into force last 25 May 2018. Liège University Ethics Committee's approval was obtained (ref. 2012/277) and all subjects signed the informed consent.

3. Results

From the 534 total participants of the SarcoPhAge cohort at baseline, the blood samples needed to assess inflammation and calculate the GLIM criteria were available for 411 (77%) individuals. From them, 373 individuals (69.8%) had data for the outcome "death" available during the 5-year follow-up, and 38 were unavailable by phone or postal survey becoming impossible to get to know about their living status, therefore, they were considered as lost during the follow-up. These 373 individuals (73.07 ± 5.96 years, 56% women) have been considered the study sample (Fig. 1).

Table 1 shows the clinical characteristics of the sample at baseline. Malnutrition according to the GLIM criteria was present in 91 (24.4%) individuals at baseline and it ranged from 52 (13.9%) individuals according to the GLIM criteria without muscle mass, to 78 (20.9%) individuals according to the GLIM criteria with Ishii's score chart when applying the 7 pragmatic approaches.

Table 2 shows the 5-year mortality risk for subjects with baseline malnutrition according to the GLIM criteria and the 7 pragmatic approaches. Subjects that met the GLIM criteria had a significant increase in mortality risk, HR: 3.78 (95% Confidence Interval (CI): 2.19–6.53), and that increase was consistent in the adjusted model for age, sex, number of concomitant diseases, number of drugs, level of physical activity and cognitive status as covariates: HR 3.38 (95% CI: 1.89–6.04). Subjects that met any of the 7 pragmatic approaches had also a significant increased risk of mortality both in crude and adjusted model. In the adjusted model, the HR ranged between the lowest HR obtained by Goodman grid HR: 2.72 (95% CI 1.51–4.91) and the highest obtained by Ishii's score chart HR: 3.94 (95% CI 2.14–7.24).

The performance indicators of the 7 pragmatic approaches of the GLIM criteria compared to the original GLIM criteria as the gold standard are showed in Table 3. The lowest sensitivity was obtained by the GLIM criteria without a reduced muscle mass [sensitivity = 57.14 (95% CI 46.34 to 67.47)] and the highest by the GLIM criteria with Ishii's score chart [sensitivity = 71.43 (95% CI 61.00 to 80.41)], which is coherent with the lowest and the highest prevalence of malnutrition obtained when applying these two approaches, respectively. All of the 7 approaches obtained a specificity ≥95%, which ranged from specificity = 95.39 (95% CI 92.25 to 97.52) obtained by the GLIM criteria with Ishii's score chart to specificity = 99.30 (98.70–99.91) obtained by the GLIM criteria without a reduced muscle mass.

All the 7 approaches obtained a high PPV, which ranged from the PPV = 83.33 (95% CI 74.35 to 89.62) obtained by the GLIM criteria with Ishii's score chart to PPV = 96.30 (95% CI 86.60 to 99.05) obtained by the GLIM criteria without a reduced muscle mass. The 7 approaches also obtained a high NPV, with ranged from NPV = 87.85 (95%CI 85.08 to 90.17) obtained by the GLIM criteria without a reduced muscle mass and NPV = 91.19 (95% CI 88.19 to 93.48) by Ishii's score chart. Therefore, all the 7 approached showed fair diagnostic performance indicators.

3The AUC was ≥0.7 for all the approaches (Fig. 2), ranged from AUC = 0.654 (95%CI 0.592 to 0.716) obtained by the GLIM criteria with Yu's formula to AUC = 0.760 (95%CI 0.706 to 0.815) obtained by the GLIM criteria with calf circumference. Ishii's score chart had the highest sensitivity (71.4%), NPV (91.19%), and an AUC (0.735).

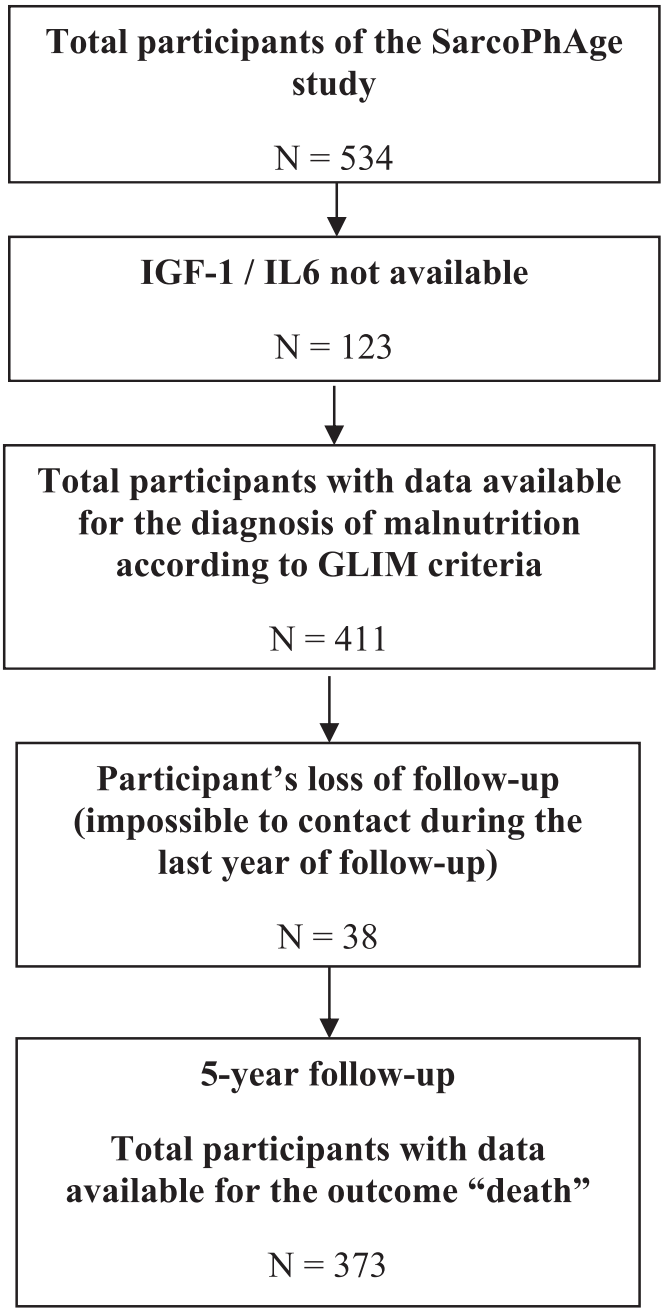

Fig. 1. Flow chart of the SarcoPhAge study during the 5-year follow-up.

The concordance between the GLIM criteria as gold standard and the 7 pragmatic approaches and the concordance among all of them is showed in Table 4. A strong concordance has been found between the original GLIM criteria and the 7 approaches, meaning that both identified almost the same individuals. The values of Cohen kappa coefficient ranged from k = 0.667 (0.617–0.715, strong concordance) between the GLIM criteria and the GLIM criteria with Goodman's grid to k = 0.724 (0.678–0.769, strong concordance) between the GLIM criteria and the GLIM criteria with calf-circumference.

The results obtained in the TELOS-feasibility assessment are showed in Table 5. The GLIM criteria showed a TELOS-feasibility score = 3 and the 7 pragmatic approaches obtained TELOS-feasibility scores ranging from 6 to 7.

Table 1
Baseline characteristics of study participants in the SarcoPhAge study according to GLIM criteria and the 7 pragmatic approaches (n = 373).

	Whole studied sample	Malnutrition according to the GLIM criteria	GLIM criteria without muscle mass as criterion	GLIM criteria with calf circumference	GLIM criteria with handgrip strength	GLIM criteria with Ishii's score chart	GLIM criteria with mid-arm circumference	GLIM criteria with Yu's formula	GLIM criteria with Goodman grid
	373 (100%)	Yes (n = 91)	Yes (n = 52)	Yes (n = 70)	Yes (n = 64)	Yes (n = 78)	Yes (n = 70)	Yes (n = 73)	Yes (n = 58)
Prevalence of malnutrition (%)	–	24.4%	13.9%	18.8%	17.2%	20.9%	18.8%	19.6%	15.6%
Age, years	73.07 ± 5.96	73.30 ± 6.63	74.69 ± 6.71	74.70 ± 6.70	74.83 ± 7.14	75.73 ± 6.93	74.95 ± 6.94	74.92 ± 6.81	74.24 ± 6.78
Sex (n, %)									
Women	209 (56)	60 (65.9)	32 (61.5)	44 (62.9)	42 (65.6)	55 (70.5)	48 (68.6)	48 (65.8)	34 (58.6)
Body mass index, kg/m^2	26.78 ± 4.66	23.92 ± 3.82	24.04 ± 4.35	24.04 ± 4.35	24.13 ± 4.74	24.38 ± 4.41	24.03 ± 4.39	23.95 ± 4.21	23.57 ± 4.64
Fat-free mass, kg									
Women	38.94 ± 6.40	35.52 ± 6.62	35.22 ± 8.23	35.37 ± 7.34	35.56 ± 7.81	35.62 ± 7.05	35.47 ± 7.14	34.84 ± 7.06	35.19 ± 8.11
Men	56.73 ± 8.60	49.47 ± 8.26	50.21 ± 9.03	49.41 ± 8.55	49.94 ± 8.84	49.07 ± 8.73	50.29 ± 9.35	48.44 ± 8.59	50.21 ± 8.21
FFMI, kg/m^2									
Women	15.38 ± 1.89	14.27 ± 2.27	14.28 ± 3.01	14.52 ± 2.68	14.59 ± 2.81	14.85 ± 2.58	14.64 ± 2.62	14.69 ± 2.64	14.26 ± 2.96
Men	18.78 ± 2.45	17.06 ± 2.22	17.37 ± 2.77	17.33 ± 2.57	17.29 ± 2.58	17.13 ± 2.57	17.38 ± 2.65	17.05 ± 2.48	17.29 ± 2.50
ALMI, kg/m^2									
Women	6.09 ± 0.98	5.52 ± 0.72	5.71 ± 0.86	5.69 ± 0.78	5.71 ± 0.83	5.82 ± 0.97	5.71 ± 0.80	5.80 ± 1.03	5.69 ± 0.84
Men	7.92 ± 1.07	6.98 ± 0.91	7.18 ± 1.08	7.06 ± 1.01	7.12 ± 1.03	7.07 ± 1.03	7.16 ± 1.04	7.01 ± 0.99	7.16 ± 0.98
Number of concomitant diseases per subject	4 (3–6)	5 (4–7)	5 (4–7)	5 (4–7)	5 (4–7)	5 (3–7)	5 (3–7)	5 (3.5–7)	5 (3–7)
Number of drugs per subject	5 (3–8)	6 (4–9)	6 (4–9)	6 (4–9)	6 (4–10)	6 (4–9)	6 (4–8.25)	6 (4–9)	6 (3–8.25)
MMSE (/30)	29 (28–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)
IADL Lawton									
/8 for women	8 (8–8)	8 (7,8)	8 (6.5–8)	8 (7,8)	8 (6.75–8)	8 (7,8)	8 (7,8)	8 (7,8)	8 (6.75–8)
/5 for men	5 (5–5)	5 (5–5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)	5 (4,5)
Gait speed, m/s	0.99 ± 0.28	0.85 ± 0.33	0.85 ± 0.33	0.86 ± 0.30	0.83 ± 0.31	0.84 ± 0.29	0.86 ± 0.31	0.86 ± 0.31	0.88 ± 0.33
SPPB (/12)	10 (8–11)	9 (6–11)	9 (6–11)	9 (6–11)	8 (6–10)	8 (6–10)	9 (6.75–11)	9 (6.5–11)	9 (6–11)
Muscle strength (kg)									
Women	21.87 ± 6.79	20.03 ± 5.61	19.56 ± 6.14	19.36 ± 6.03	17.79 ± 6.50	17.82 ± 5.72	19.23 ± 6.41	18.82 ± 6.24	19.27 ± 6.12
Men	39.25 ± 8.88	33.36 ± 10.72	33.82 ± 10.14	33.9 ± 9.81	31.52 ± 11.40	31.46 ± 11.12	34.40 ± 10.93	33.52 ± 10.04	35.56 ± 10.37
Sarcopenia EWGSOP2 (n, %)	15 (4.0)	13 (14.3)	7 (13.5)	8 (11.4)	13 (20.3)	12 (15.4)	10 (14.3)	11 (15.1)	7 (12.1)
Insulin-growth factor 1 (ng/mL)[a]	105.2 (84.6–131.5)	89.3 (73.7–119.7)	89.1 (73.6–121.4)	89.7 (67.3–118.6)	90.0 (77.3–121.4)	87.7 (73.6–119.0)	88.5 (76.6–118.6)	91.1 (75.4–119.8)	91.0 (77.5–122.5)
Interleukin-6 (pg/mL)[b]	1.86 (0.73–3.49)	3.11 (1.26–6.63)	3.15 (1.18–6.34)	3.32 (1.24–6.61)	3.30 (1.21–6.61)	3.15 (1.19–5.94)	3.22 (1.19–5.97)	3.13 (1.23–6.58)	3.15 (1.14–6.6)
Quality of life									
SF-36 PCS (/100)	44.7 (37.1–51.6)	40.8 (34.8–48.3)	39.1 (31.8–46.6)	39.4 (32.9–46.6)	38.3 (30.5–46.1)	39.0 (32.1–46.4)	39.4 (32.9–47.9)	40.0 (32.7–46.0)	40.0 (32.2–49.9)
SF-36 MCS (/100)	45.0 (35.5–53.4)	40.6 (33.2–52.4)	38.3 (31.9–46.7)	39.0 (32.4–49.1)	38.7 (31.9–48.9)	38.8 (32.1–48.6)	40.2 (32.9–52.1)	38.7 (32.0–48.8)	38.9 (32.4–49.3)
EuroQol 5D	0.81 (0.70–0.82)	0.79 (0.51–0.82)	0.78 (0.46–0.84)	0.78 (0.46–0.84)	0.78 (0.46–0.84)	0.80 (0.47–0.83)	0.80 (0.46–0.84)	0.80 (0.46–0.83)	0.80 (0.46–0.84)

ALMI: Appendicular lean mass index; **EWGSOP2:** Revised European consensus on definition and diagnosis; **FFMI:** Fat-free mass index; **GLIM:** Global Leadership Initiative on Malnutrition; **IADL:** Instrumental activities of daily living (Lawton); **MMSE:** Mini-Mental State Examination; **MNA**: Mini-Nutritional Assessment**; MSC score:** Mental composite score; **PSC** score: Physical composite score; **SF**: Short Form; **SPPB:** Short Physical Performance Battery. Age, BMI, fat-free mass, fat free mass index, ALMI, muscle strength, gait speed had a normal distribution and were expressed by mean and SD. All the other ones were skewed and expressed by median (P25–P75).

[a] **IGF-1 levels** were divided into sex-specific quartiles (C1–C4) calculated in our sample and the lowest quartile was selected as a cut-off point for our study. Men: **C1 ≤ 88 ng/mL**, C2: 89–106 ng/mL, C3: 107–134 ng/mL, C4: ≥135 ng/mL; **women: C1 ≤ 82 ng/mL**, C2: 83–103 ng/mL, C3: 104–127 ng/mL, C4: ≥128 ng/mL.

[b] **IL-6 levels** were divided into sex-specific quartiles (C1–C4) calculated in our sample and the lowest quartile was selected as a cut-off point for our study: >3.84 pg/mL in men; >2.99 pg/mL in women.

Table 2
Five-year incidence of deaths and its association with malnutrition at baseline according to GLIM criteria and the 7 pragmatic approaches.

	Studied sample	**Malnutrition according to the GLIM criteria**				
	N = 373	**Yes (n = 91)**	**No (n = 282)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	26 (26.8)	26 (9.22)	3.78 (2.19–6.53)	4.41 (2.51–7.76)	3.38 (1.89–6.04)
	Studied sample	**Malnutrition according to GLIM criteria without a reduced muscle mass**				
	N = 373	**Yes (n = 52)**	**No (n = 321)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	18 (34.6)	34 (10.6)	4.09 (2.30–7.24)	4.16 (2.29–7.54)	3.09 (1.67–5.70)
	Studied sample	**Malnutrition according to GLIM criteria with calf circumference**				
	N = 373	**Yes (n = 70)**	**No (n = 303)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	24 (34.3)	28 (9.24)	4.75 (2.75–8.21)	4.63 (2.63–8.15)	3.35 (1.85–6.07)
	Studied sample	**Malnutrition according to GLIM criteria with handgrip strength**				
	N = 373	**Yes (n = 64)**	**No (n = 309)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	20 (31.2)	32 (9.71)	3.71 (2.12–6.49)	3.89 (2.15–7.06)	2.78 (1.50–5.16)
	Studied sample	**Malnutrition according to GLIM criteria with Ishii's score chart**				
	N = 373	**Yes (n = 78)**	**No (n = 295)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	26 (35.9)	26 (8.81)	4.70 (2.72–8.10)	5.24 (2.89–9.49)	3.94 (2.14–7.24)
	Studied sample	**Malnutrition according to GLIM criteria with mid-arm circumference**				
	N = 373	**Yes (n = 70)**	**No (n = 303)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	23 (32.8)	29 (9.57)	4.15 (2.40–7.18)	4.82 (2.68–8.66)	3.69 (2.02–6.72)
	Studied sample	**Malnutrition according to GLIM criteria with Yu's formula**				
	N = 373	**Yes (n = 73)**	**No (n = 300)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	25 (34.2)	27 (9.00)	4.75 (2.76–8.20)	4.75 (2.68–8.42)	3.53 (1.95–6.39)
	Studied sample	**Malnutrition according to GLIM Criteria with Goodman grid**				
	N = 373	**Yes (n = 58)**	**No (n = 315)**	**Crude HR (95%CI)**	**Model 1 HR (95%CI)**	**Model 2 HR (95% CI)**
Five-year incidence of deaths (n, %)	52 (12.9)	29 (50.0)	33 (10.5)	3.78 (2.15–6.65)	3.25 (1.82–5.83)	2.72 (1.51–4.91)

Model 1: Age and sex as covariates.
Model 2: Age, sex, number of concomitant diseases, number of drugs, physical activity level, and cognitive status as covariates.
Because survival data were available, we applied the COX proportion hazards model giving the hazard ration (HR) and 95% confidence interval (CI).

Table 3
Performance indicators of the 7 pragmatic approaches of GLIM criteria compared to GLIM criteria (gold standard).

	Se (%) 95% CI	Sp (%) 95% CI	PPV (%) 95% CI	NPV (%) 95% CI	AUC 95% CI
GLIM criteria without a reduced muscle mass	57.14 46.34 to 67.47	99.30 98.70 to 99.91	96.30 86.60 to 99.05	87.85 85.08 to 90.17	–
GLIM criteria with calf circumference	69.23 58.68 to 78.49	97.52 94.95 to 99.00	90.00 81.05 to 94.99	90.76 87.82 to 93.04	0.760 0.706 to 0.815
GLIM criteria with handgrip strength	64.84 54.12 to 74.56	98.23 95.91 to 99.42	92.19 83.01 to 96.61	89.64 86.75 to 91.97	0.663 0.601 to 0.725
GLIM criteria with Ishii's score chart	71.43 61.00 to 80.41	95.39 92.25 to 97.52	83.33 74.32 to 89.62	91.19 88.19 to 93.48	0.735 0.679 to 0.792
GLIM criteria with mid-arm circumference	65.93 55.25 to 75.55	96.45 93.58 to 98.29	85.72 76.23 to 91.82	89.77 86.82 to 92.12	0.733 0.674 to 0.792
GLIM criteria with Yu's formula	69.57 59.10 to 78.73	96.81 94.03 to 98.53	87.67 78.66 to 93.20	90.70 87.74 to 93.00	0.654 0.592 to 0.716
GLIM criteria with Goodman grid	60.44 49.64 to 70.54	98.94 96.92 to 99.78	94.83 85.46 to 98.28	88.75 85.73 to 90.90	0.734 0.677–0.791

AUC: Area under the ROC curve; **GLIM:** Global Leadership Initiative on Malnutrition; **Se**: sensitivity; **Sp**: specificity; **PPV**: positive predictive value; **NPV**: negative predictive value.

4. Discussion

Our study showed that the GLIM criteria and the 7 pragmatic approaches predicted three-to four-fold mortality in older community-dwelling population during a 5-year follow-up. Moreover, the pragmatic approaches had correct performance indicators, and were feasible. The prevalence of malnutrition with the original GLIM criteria was 24.4%, while with the pragmatic approaches were 20.9%–13.9%, which might underestimate prevalence, particularly for the approach "GLIM criteria without a reduced muscle mass", which was the less accurate and less associated with mortality. However, it is important to highlight that, with this exception, all of them had excellent prognosis capability for mortality, ensured an accurate diagnosis, predicted mortality, and can be implemented in clinical practice.

The scientific community has faced the challenge of applying the consensus-based GLIM criteria to predict mortality. Contreras et al. [54], applied the GLIM criteria with handgrip strength and their results found an Odds Ratio of 2.72, (CI 1.37–5.40) to predict 6-month mortality in hospitalized advanced cancer patients [54]. Sanz-Paris et al., applied the GLIM criteria with calf and mid-arm circumference in older patients with diabetes mellitus and they found that having severe malnutrition at baseline doubled the risk of mortality during the 8-year follow-up [24].

Our study might have an impact towards the widespread diffusion of the new GLIM criteria for three reasons; first, our study showed that the GLIM criteria are capable to predict mortality, validated the approaches proposed by the GLIM in the original publication, and showed that the 7 pragmatic approaches were feasible. Importantly, the use of the pragmatic approaches did not

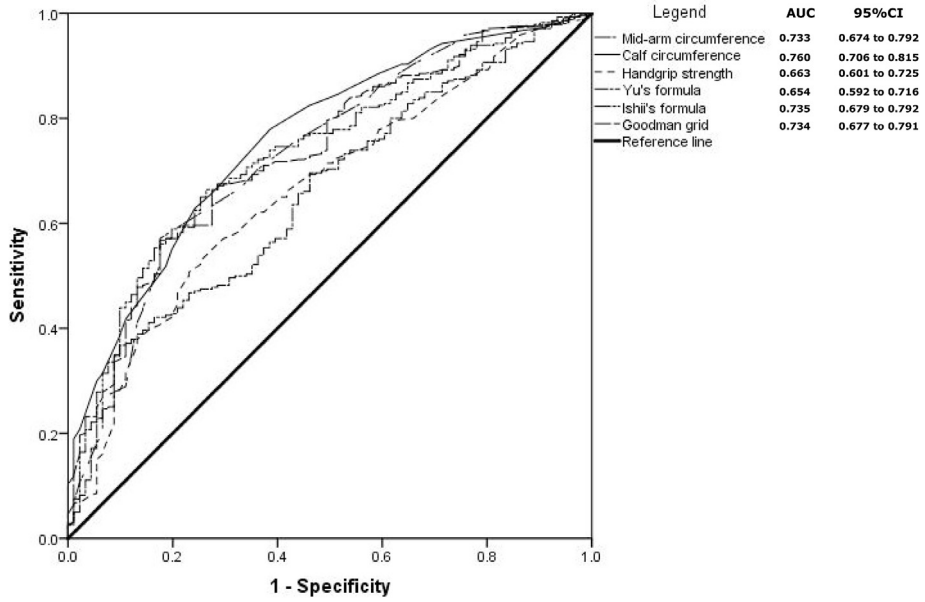

Fig. 2. Area under the ROC curve analysis for subjects with baseline malnutrition according to the GLIM criteria and the 7 pragmatic approaches.

Table 4
Concordance between GLIM criteria and the 7 pragmatic approaches.

	GLIM criteria	GLIM criteria without a reduced muscle mass	GLIM criteria with calf circumference	GLIM criteria with handgrip strength	GLIM criteria with Ishii's score chart	GLIM criteria with mid-arm circumference	GLIM criteria with Yu's formula	GLIM criteria with Goodman grid
GLIM criteria	1							
GLIM criteria without a reduced muscle mass	0.668 0.618 to 0.716	1						
GLIM criteria with calf circumference	0.724 0.678 to 0.769	0.824 0.781 to 0.861	1					
GLIM criteria with handgrip strength	0.701 0.651 to 0.747	0.878 0.840 to 0.909	0.782 0.737 to 0.823	1				
GLIM criteria with Ishii's score chart	0.702 0.655−0.748	0.760 0.713 to 0.802	0.798 0.754 to 0.838	0.861 0.822 to 0.894	1			
GLIM criteria with mid-arm circumference	0.677 0.626 to 0.724	0.824 0.781 to 0.861	0.824 0.781 to 0.861	0.818 0.775 to 0.856	0.815 0.772 to 0.853	1		
GLIM criteria with Yu's formula	0.720 0.671 to 0.765	0.799 0.755 to 0.838	0.853 0.813 to 0.887	0.812 0.769 to 0.850	0.859 0.819 to 0.893	0.853 0.813 to 0.887	1	
GLIM criteria with Goodman grid	0.667 0.617 to 0.715	0.936 0.906 to 0.959	0.793 0.748 to 0.833	0.824 0.781 to 0.861	0.732 0.684 to 0.776	0.793 0.748 to 0.833	0.788 0.743 to 0.828	1

have any negative impact in the quality of the diagnosis compared to the original GLIM criteria. Second, a call action to solve the gap between research and clinical practice and to validate pragmatic approaches had been already pointed out by the GLIM, ESPEN, and EuGMS [55]. This validation study was needed, as despite of the support of the ESPEN and EuGMS to the new criteria, and the interest that the new definition has aroused among the European geriatric societies, there are still no national European guidelines that recommend the GLIM criteria [43]. The pitfall of measuring muscle mass [16], the lack of the technical devices to measure it in most of clinical settings [17](43), and the lack of reimbursement of that procedure had been pointed out as a challenge, i.e., by the Spanish Society of Physical Medicine and Rehabilitation [56].

The pragmatic approaches to be included as surrogates of muscle mass and their thresholds were chosen on the basis of three requirements: First, the pragmatic approach had to be applicable in settings with limited resources (from a technical, economical, knowledge, effort, and time point of view); second, they had to be evidence-based, externally validated in other cohorts apart of SarcoPhAge, and finally, the data had to be available in our database at baseline for the post-hoc analysis. Wide evidence was found for calf-circumference and for its threshold <31 cm [31,57,58], and that was our rationale to choose them. The lowest quartile for calf-circumference in our sample was calculated and it is 32.5 cm, which is quite close to the <31 cm threshold from MNA test reference and does not modified substantially the results, so, the threshold already acknowledged as a reference was used for the analysis.

About mid-arm circumference, we were actually interested in including upper arm, in order to avoid the eventual biases of the use of lower limbs, where the frequent occurrence of edema might limit its use in acute process, cardiorespiratory diseases, or immobilized patients, among others. Moreover, upper arm is usually more accessible during physical examination and does not require an extra time for each outpatient visit, i.e. in outpatients' clinics. However, to authors' knowledge, mid-arm circumference in older people lacks of standardized value, therefore, the lowest quartile (<21 cm value) was calculated for our sample. This value in SarcoPhAge might be a reference for further research and clinical use.

Table 5
Feasibility of the GLIM criteria and the 7 pragmatic approaches using the TELOS model.

TELOS model components			GLIM criteria	GLIM criteria without a reduced muscle mass	GLIM criteria with calf circumference	GLIM criteria with handgrip strength	GLIM criteria with Ishii's score chart	GLIM criteria with mid-arm circumference	GLIM criteria with Yu's formula	GLIM criteria with Goodman grid
T	Technology	Is the tool available in the clinical setting?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Is staff trained to implement the new assessment method?	No	Yes	Yes	Yes	No	Yes	No	No
E	Economics	Is the cost of training acceptable?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Is the training period less than 1 h?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
L	Legal	Does the assessment conflict with legal requirements?	No	No	No	No	No	No	No	No
O	Operational	Does the assessment method solve a clinical problem? Is muscle assessment required in clinical practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S	Scheduling	Does the procedure take less time than the current standard method of measurement?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total score Feasibility if total score ≥3			3	7	7	6	6	7	6	6

A positive response ("Yes") in a component scores 1 and a negative response ("No") scores 0. "No" in the Legal component is mandatory and this component does not compute in the total score. Feasibility was defined as a total score ≥3.

It is important to highlight that muscle depletion and sarcopenia are different entities [2,15,59]. Muscle depletion or reduced muscle mass is one of the phenotypic criteria for the GLIM, but it is not the same as sarcopenia, which necessarily involves the loss of function. According to EWGSOP2, low strength (e.g. handgrip) indicates probable sarcopenia, when combined with reduced muscle mass sarcopenia is confirmed, and when function is low (e.g. gait speed) severe sarcopenia is present [14]. Although sarcopenia does not use inflammation as a defining criterion, inflammation is often linked to (and causative of) sarcopenia [2,60]. The difference between these two concepts was depicted in the ESPEN guidelines on definition and terminology of clinical nutrition, which includes a conceptual tree of malnutrition and nutrition-related diseases, from the basic definition of malnutrition to aetiology-based diagnoses [60]. Regarding the longitudinal relationships between the two diseases, malnutrition according to GLIM criteria at baseline has been associated to a four-fold higher risk of the onset of sarcopenia in the SarcoPhAge study during a 4-year follow-up in a recent publication of our research group [1]. However, further research is needed on the association between sarcopenia at baseline and the onset of malnutrition according to GLIM criteria during a longitudinal follow-up. This was planned as one of the aims of the study, but has not been conducted yet due to budget limitations. A recent retrospective study in patients from 18 hospitals in Canada explored the diagnostic performance indicators of several combinations of the phenotypic and etiologic criteria, and also including fewer or higher number of criterion and used the subjective global assessment (SGA) as gold standard. Applying all criteria that compose the GLIM definition together, against SGA, obtained a sensitivity of 61.3%; other possible combinations with fewer number of criteria showed much lower sensitivity, e.g., the combination of weight loss AND high CRP had the highest sensitivity (46.33%) with a specificity of 93.02% (PPV: 84.54%; NPV: 67.80%), and the combination of low BMI AND low intake had much lower sensitivity (15.54%) with the highest specificity (98.84%). Authors concluded that applying a limited number of criterion might lead to missing out a high percentage of malnourished patients, and therefore, underdiagnose and undertreat a reversible disease [61]. These results are aligned with the conclusions of our study, where the 6 pragmatic approaches that included a substitute of muscle mass had higher sensitivity and better diagnostic performance indicators than the simply omission of muscle mass within the criteria. Likewise, the EAMA 9+ study is an ongoing European collaborative project aimed on assessing nutrition-related diseases in acute clinical healthcare settings; the protocol of the study has been published an includes the assessment of malnutrition according to GLIM criteria with handgrip strength and calf circumference [62].

A strength of our study is the use of mortality as main outcome, as it is the most robust health adverse consequence. Moreover, the study provides a wide range of solutions for those clinicians that would like to assess their patients' nutritional status with updated tools in order to provide best quality of care [43]. Another strength of our study is the inclusion of a feasibility score. Despite available data about the future prevalence of sarcopenia in Europe [63] and the health economic burden of sarcopenia [64], to authors' knowledge studies about feasibility of health interventions are scarce [42,65] and no feasibility study about the assessment of nutrition-related diseases in clinical practice exists. Feasibility studies might provide solid and objective indicators to guide the implementation of diagnostic and therapeutic interventions [65].

Two different types of limitations should be acknowledged; one is derived from the post-hoc nature of our study. First, we were unable to include SARC-F among the pragmatic approaches. The reason is that SARC-F was published in 2013, after the date of

baseline assessment of the SarcoPhAge cohort. Despite SARC-F having been administered along the follow-up of the cohort [19], unfortunately, there are not enough data to calculate the score at baseline retrospectively in the SarcoPhAge study. This lack of available data also affected the inclusion of SARC-CalF 31 and SARC-CalF 33 [57] in our study, and assessing their prognosis capability and diagnostic properties as substitute of muscle mass for GLIM criteria could be an interesting topic for further research. Second, unintentional weight loss >4.5 kg in the past year was used as a threshold for unintentional weight loss [30], which slightly differs from the amount of weight loss over time recommended by the GLIM (def. >5% in 6 months or >10% beyond). Authors consider that this is a minor issue, as weight loss >4.5 kg in the past year has been shown to be a strong predictor of mortality in the Cardiovascular Health Study, among others [30,66]. Moreover, the other two phenotypic criteria were applied as indicated in the original GLIM criteria, therefore, it is unlikely that the small modification in that criterion causes an impact in the prevalence of malnutrition at baseline in the SarcoPhAge study. A recent survey among specialists in Geriatric Medicine from 14 European countries, showed that unintentional weight loss was the phenotypic criterion most frequently recommended in national guidelines about malnutrition. However, there was not consistency in the relevant time-period for over which to consider weight loss, which varied widely [43]; the percentages proposed by GLIM would be an opportunity to harmonize the thresholds to consider a weight loss as clinically relevant. Third, regarding the etiologic criteria, disease burden and food assimilation were not assessed in the study, and it could be considered as a limitation. Finally, all participants in our sample were assessed for malnutrition and the first screening step was omitted for study purposes, in order to include the largest possible sample for the calculation of muscle mass. The direct consequence was that the overall prevalence of malnutrition obtained was larger than the one expected by the GLIM for community-dwelling older people. In fact, it is very likely that the prevalence is, in reality, smaller than 24%, since previous studies (using other tools than the GLIM) indicate that around 5–10 percent of community-dwelling older people are malnourished [67]. Although the omission of the first screening step could be considered as a limitation, this issue does not discriminate the interest of the study, which provides new evidence about the comparison of different pragmatic ways to calculate and define loss of muscle mass. The calculation of the severity grading was also not possible due to the use of the modified threshold for weight loss; to authors' knowledge, only the study from Allard et al., has assessed severity of malnutrition according to the GLIM [61], and exploring severity grading could be a challenging topic for further research.

The other type of limitations of our study is related to the study cohort design. The inclusion of general community-dwelling older people might involve a selection bias that has been previously reported in cohorts of community-dwelling older people [68] and in the SarcoPhAge study [1]. The characteristics of voluntary older participants (motivation, involvement in self-care management in musculo-skeletal health, etc.) might differ from those who refused to get involved in a research study. Moreover, volunteers recruited were relatively young at baseline, able to walk, without cognitive impairments, and their health status might be better than the general Belgian population of the same age. These eventual biases could have affected the prevalence of malnutrition in our sample, which could be higher in the general older population. The relatively young age and stable overall status is also a strength of the study, as the findings might have higher external validity for general population. Finally, the diseases and the drugs taken by the participants were not listed and this has to be acknowledged as a limitation of our work. However, the number of drugs and number of diseases were recorded in absolute numbers, and they were used as confounders for the analysis.

The overall study was conceived to bridge the gap between research and clinical practice and to provide evidence-based solutions for current unmet needs in clinical practice ("Action-research philosophy", "from bedside to bench, to bedside again") [25]. Our study might be helpful to better align the interests of the National scientific societies with the interest of the largest societies of clinical nutrition (ESPEN, SSCWD, etc.), EuGMS, etc., as they might be able to endorse the GLIM criteria by now, as they have been shown their predictive capacity for mortality, and there are feasible options available that could improve nutritional care.

Conclusions

Our study provided 7 pragmatic approaches of the GLIM criteria which predicted three-to four-fold mortality during a 5-year follow-up, showed adequate performance indicators, almost-perfect or strong concordances with the original ones, and were feasible. Clinicians would be free to decide among a wide range of GLIM pragmatic approaches that predict mortality, ensure an accurate diagnosis, and are feasible in clinical settings.

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Credit authors statement

DSR, ML and CB wrote the manuscript; DSR did literature review; ML, LL, and CB participated in data collection; ML and CB analyzed and interpreted data; JYR, EC, OB, and CB corrected the manuscript. All co-authors read and approved the final version of the manuscript.

Conflict of Interest

All authors declare they do not have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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