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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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Abstract:	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 (Sarcopenia and Physical 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.

To N. E. P. Deutz MD PhD,

Editor in-Chief of *Clinical Nutrition*

Dear Dr. Deutz:

Thank you for your attention to our work and for giving us the opportunity to revisit it again. Please find enclosed the response to reviewer 3 and the revised version of our manuscript YCLNU-D-20-00315, "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". All reviewer's comments have been addressed and authors agree that they significantly improved the manuscript. We hope our manuscript is now suitable for publication in *Clinical Nutrition* as an original article.

This manuscript has not been previously reported and it is not under consideration for publication elsewhere. Written permission of all authors has been obtained. Correspondence about the paper should be directed to the corresponding author at the following address:

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Thank you for your attention to our manuscript.
Sincerely,

Dolores Sanchez-Rodriguez MD PhD on behalf of the authors

Response to Reviewer 3 comments

Reviewer 3: This paper on seven pragmatic approaches to calculate and define loss of muscle mass for defining malnutrition according to the GLIM criteria is interesting and provide practical guidelines that are needed since the original GLIM paper is vague in the management of this criterion. The provided information can be used for future revisions of the GLIM format. There are still room for justifications and amendments:

COMMENT 1, major remark. The major issue is that it has to be more clearly stated that the malnutrition prevalence figures are calculated without the first (and important) screening step in the process of defining malnutrition according to the GLIM format. The 2-step process of GLIM is advocated in order for screening to identify those "at risk" of malnutrition (according to any validated screening tool), and next to confirm malnutrition by the GLIM criteria. Screening is for sensitivity, whereas confirmation is for specificity. It is likely that the prevalence figure in reality is smaller than 24%, which is to be expected since previous studies (using other tools than GLIM) indicate that around 5-10 percent of community-dwelling older people are malnourished. Still, this remark does not discriminate the study since the importance of the study is the comparison of different pragmatic ways to calculate and define loss of muscle mass.

AUTHORS RESPONSE: The authors actually appreciate the reviewer's positive feedback about the study, and the fact of considering that it contains valuable evidence for the future revisions of the GLIM format.

The authors agree with the reviewer that the main interest of the study is the new evidence about the impact of different practical methods to calculate and define loss of muscle mass on the prediction of mortality. The reasons for not applying the first-step screening proposed by the GLIM was that first, we wanted to include the largest number possible of participants in the analyses and second, we had the systematic assessment of body composition and muscle mass by DXA available in the whole study sample of the SarcoPhAge study at baseline.

The reviewer is right; applying the screening would have shown a different, lower prevalence. The above-mentioned reasons and the methodology to calculate the

prevalence have been clearly explained in the method section of the revised version of our manuscript. Moreover, both, the reason (i.e. to include a largest sample for purpose of analysis) and its direct consequence (i.e. largest prevalence), have been clarified and discussed in the discussion section and acknowledged as a limitation in the revised version of the manuscript.

Methods (page 6, line 115-121): "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."

Discussion (page 21, lines 457-466): "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. 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."

Minor remarks. COMMENT 2: The title of the manuscript could become somewhat clearer: "Prediction of 5-year risk of mortality by malnutrition according to the GLIM format using seven pragmatic approaches to define the criterion of loss of muscle mass"

AUTHORS RESPONSE: The title of the new manuscript has been rewritten according to the reviewer's suggestion, which has been also used to improve some phrases in the abstract and the manuscript. Thank you.

Title: "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."

Abstract. Introduction: ..." the GLIM format, using seven pragmatic approaches to define the criterion of loss of muscle mass."

Secondary objective (page 5, line 92-94): "Secondarily, we assessed the prevalence, diagnostic performance indicators, and concordance of the 7 pragmatic approaches, compared to the original GLIM criteria."

Highlights (page 24, line 500): "GLIM and the 7 pragmatic approaches to define muscle loss predicted...."

COMMENT 3. Line 63-64: Is it true that GLIM proposed omission of muscle mass as one option? I don't think so.

AUTHORS RESPONSE: The reviewer is right, sorry for this lack of attention. This phrase has been corrected, as follows:

Introduction (page 6, line 63-64): "..., GLIM proposed pragmatic approaches: Substituting a phenotypic criterion like calf-circumference or mid-arm circumference, or handgrip strength for muscle mass."

COMMENT 4. Lines 386-: 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 at hand.

AUTHORS RESPONSE: The reviewer is right, sorry for this lack of attention in the discussion. The paragraph has been corrected:

Discussion (page 19, line 392-3994: "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".

COMMENT 5. Line 389: Although sarcopenia does not use inflammation as a defining criterion, inflammation is often linked to (and causative of) sarcopenia.

AUTHORS RESPONSE: The reviewer is right. The phrase has been improved following your guidance, as follows:

Discussion (page 19, line 394): "Although sarcopenia does not use inflammation as a defining criterion, inflammation is often linked to (and causative of) sarcopenia."

COMMENT 6. Line 484: Add "GLIM and the 7 pragmatic approaches to define muscle loss predicted…."

AUTHORS RESPONSE: The phrase has been corrected. Thank you.

Highlights (page 24, line 500): "GLIM and the 7 pragmatic approaches to define muscle loss predicted…."

1   **Prediction of 5-year mortality risk by malnutrition according to the GLIM format using**

2   **seven pragmatic approaches to define the criterion of loss of muscle mass**

3   **Abstract**

4   **Objectives:** To assess the association between baseline malnutrition according to the GLIM

5   format, using seven pragmatic approaches to define the criterion of loss of muscle mass, with

6   mortality in the SarcoPhAge (*Sarco*penia and *Ph*ysical Impairment with advancing *Age*) study

7   during a 5-year follow-up. Secondarily, to calculate diagnostic performance indicators,

8   concordance, and feasibility of these 7 pragmatic approaches compared to the original GLIM

9   criteria.

10   **Methods:** Post-hoc analysis of the SarcoPhAge cohort, which included 534 community-

11   dwelling volunteers ≥65-year-old, followed-up from 2013 to 2019. Baseline malnutrition was

12   defined by GLIM criteria and 7 approaches: 1) Omission of a reduced muscle mass as a

13   criterion; 2) Substitution for handgrip strength, 3) Calf-circumference, 4) Mid-arm

14   circumference, 5) Goodman's grid, 6) Ishii's score chart, and 7) Yu's formula. The

15   association between malnutrition (according to GLIM criteria and the 7 approaches) and

16   mortality was assessed by Cox-regressions. Sensitivity, Specificity, Positive (PPV), Negative

17   (NPV) predictive values, area under the curve (AUC), Cohen-kappa coefficient, and TELOS-

18   feasibility score were calculated.

19   **Results:** Data to calculate GLIM criteria were available for 373 subjects (73.07±5.96 years,

20   56% women). Prevalence of malnutrition with GLIM criteria was 24.4% (ranged from 13.9%

21   to 20.9% with the 7 approaches). GLIM criteria showed a HR=3.38 (1.89-6.09) to predict

22   mortality during the 5-year follow-up, which ranged from HR=2.72 (1.51-4.91) to 3.94 (2.14-

23   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.

Keywords: Malnutrition; GLIM; Calf-circumference; Ishii; mortality; SarcoPhAge.

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)(5)(6)(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 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

3

54 reduced muscle mass] AND at least one etiologic criterion (reduced food intake or
55 assimilation and disease burden or inflammatory conditions) (10).

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

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

76 The capacity of the GLIM criteria to predict mortality has been recently shown in hospitalized
77 patients with cancer (23) and in older patients with diabetes mellitus (24); however, the
78 capability of the GLIM criteria to predict mortality in community-dwelling older population

4

79 remains unexplored. Moreover, the impact of the presence or the omission of muscle mass as

80 part of the definition is still unknown and there are no data about the performance indicators

81 of any pragmatic approach compared with the original GLIM criteria. Our hypotheses are that

82 malnutrition according to the GLIM criteria and these 7 approaches (omission of a reduced

83 muscle mass as a phenotypic criterion, or using as substitute for muscle mass handgrip

84 strength, calf-circumference, mid-arm circumference, Goodman's grid, Ishii's score chart, or

85 Yu's formula) assessed at baseline will be capable to predict mortality in general older

86 population during a 5-year follow-up. Moreover, these 7 approaches might show good

87 performance indicators and be more feasible. Therefore, their use might bridge this gap

88 between research and clinical practice (25).

89 **Objectives:** Our primary objective was to calculate the association between baseline

90 malnutrition according to the GLIM and the 7 pragmatic approaches, with the risk of

91 mortality in community-dwelling older adults from the SarcoPhAge (*Sarco*penia and *Ph*ysical

92 Impairment with advancing Age) study during a 5-year follow-up. Secondarily, we assessed

93 the prevalence, diagnostic performance indicators, and concordance of the 7 pragmatic

94 approaches, compared to the original GLIM criteria. Finally, we explored the feasibility of the

95 GLIM criteria and the 7 approaches in clinical practice.

96

METHODS

98 The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

99 Statement was followed (26).

1. Population

101 Post-hoc analysis of a cohort study, the SarcoPhAge study, which aimed on assessing health

102 and functional adverse consequences of sarcopenia in community-dwelling older adults

103 during a 5 years follow-up. The study was conducted in Belgium and included 534 older

104 volunteers at baseline, which were annually followed-up from June 2013 to September 2019.

105 A complete protocol of the SarcoPhAge study is available (1)(27)(28).

106 **Inclusion criteria:** Community-dwelling volunteers ≥65 years old were included in the

107 SarcoPhAge cohort, with no selection criteria related to health or demographic characteristics.

108 **Exclusion criteria:** Amputated limb or body mass index (BMI) ≥50 kg/m^2. For this post-hoc

109 analysis in the SarcoPhAge cohort, two additional eligibility criteria were applied: to have the

110 variables needed to calculate the GLIM criteria available at baseline and the data of death

111 available during the 5-year follow-up. Data collection and procedures have been previously

112 described in detail (1)(28)(29).

113 **2. Diagnosis of malnutrition according to GLIM criteria:** Malnutrition according to the

114 GLIM criteria is composed by a 3-step diagnostic structure (10): screening, diagnosis, and

115 severity grading. For the purpose of analysis, diagnosis of malnutrition was applied to all

116 study sample at baseline and considered as a dichotomous variable (yes/no). Therefore, the

117 first screening step and the severity grading step proposed by the GLIM were not applied in

118 the study. The rationale for this decision was 1) because we wanted to include the largest

119 number as possible of participants in the analyses; and 2) because the assessment, at baseline,

120 of body composition and muscle mass by DXA was available in the whole study sample of

121 the SarcoPhAge study.

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

Phenotypic criteria

125 **Weight loss** (%): Body weight was measured in kilograms (kg) to the nearest 0.1 kg by

126 a precision weighbridge. Clinical interview was used to obtain unintentional weight

127 loss at baseline. Volunteers with an unintentional weight loss >4.5 kg in the past year

128 were considered meeting this phenotypic criterion (30).

129 **Low BMI** (kg/m^2): Height was measured in meters (m). BMI (kg/m^2) was calculated

130 and considered reduced if <20 kg/m^2 in <70-year-old individuals and <22 kg/m^2 in

131 ≥70-year-old (10).

132 **Reduced muscle mass:** The sum of muscle mass (fat-free mass) and muscle mass of

133 the four limbs (appendicular lean mass) was determined by daily calibrated DXA

134 (Hologic Discovery A, USA). Fat-free mass and appendicular lean mass (ALM) were

135 divided by squared height to obtain fat-free mass index (FFMI) and appendicular lean

136 mass index (ALMI) values (kg/m^2), respectively. Muscle mass was considered reduced

137 in presence of either low FFMI or low ALMI, by using the sex-related thresholds:

138 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

139 in women, following recommendations from the GLIM (10) and the EWGSOP2 (14).

Etiologic criteria

141 **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).

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

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:

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)(36)(37).

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).

3.4. 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, $0.62 \times (\text{age} - 64) - 3.09 \times (\text{handgrip strength} - 50) - 4.64 \times (\text{calf-circumference} - 42)$; score in women, $0.80 \times (\text{age} - 64) - 5.09 \times (\text{handgrip strength} - 34) - 3.28 \times (\text{calf-circumference} - 42)$. Sex-specific thresholds used were ≥105 for men and ≥120 for women (19)(20).

3.5. 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)

190 and reported by Frisancho et al., (40). The lowest quartile (a value <21 cm) was computed

191 for SarcoPhAge and used as threshold (24).

3.6. **GLIM criteria with Yu's formula:** It requires the measurement of weight and height,

193 and BMI. The appendicular skeletal muscle mass prediction equation was: 10.05+0.35

194 (weight) - 0.62 (BMI)-0.02 (age) +5.10 (if male). A value below the 20th percentile was

195 computed for SarcoPhAge and used as threshold (19).

3.7. **GLIM criteria with Goodman Grid** (22) : Goodman grids provides the probability

197 (%) of low muscle mass. It is constructed separately for men and women by using age and

198 sex-specific BMI. A threshold ≥70% in men and ≥80% in women was considered as

199 indicative of low muscle mass (22), as previously reported in SarcoPhAge (19).

4. Main outcome measure: Deaths during the 5-year follow-up in the SarcoPhAge study

201 according to the presence of malnutrition at baseline. Data for the survival curve were

202 collected annually by direct interview or assessed by medical records or phone calls with

203 relatives and caregivers if the participant did not attend the annual visit. **Secondary outcome**

204 **measures were:** 1) Diagnostic performance indicators [sensitivity, specificity, positive

205 predictive value (PPV), negative predictive value (NPV), and area under the ROC curve

206 (AUC)], and concordance (Cohen-kappa coefficient) of the 7 pragmatic approaches of GLIM

207 criteria compared to the original GLIM criteria. 2) Feasibility of the GLIM criteria and the 7

208 pragmatic approaches, measured by the Technological, Economical, Legal, Operational,

209 Schedule (TELOS)-feasibility score.

210 Feasibility was defined as "the state or degree of being easily or conveniently done (41)" and

211 explored by the TELOS-feasibility score, which assess the potential of implementation of new

212 systems. This model is used in Engineering and has been also applied into Medicine (42).

213 Five areas were assessed by polar answers (yes/no): Technological ("Is the tool available in

214 the clinical setting? Is staff trained to implement the new method?" Yes, if a training

215 infrastructure is available in the clinical setting), Economic ("Is the cost of training

216 acceptable? Is the training period less than 1 hour?" Yes, if no additional cost in terms of

217 money are needed, and less than 1 hour of training period in terms of time), Legal ("Does the

218 assessment conflict with legal requirements?"), Operational ("Does the assessment method

219 solve a clinical problem? Is muscle assessment required in clinical practice?" Yes, if

220 assessment of malnutrition is considered as relevant in clinical practice), and Schedule ("Does

221 the procedure take less time than the current standard method of measurement?" Yes, if the

222 procedure takes less than the time needed to measure muscle mass by the GLIM criteria). A

223 positive answer scores 1 point in the TELOS-feasibility score, the legal area is not included in

224 the sum up of the score, and a "no" in that area is mandatory to continue the study.

225 Interventions were considered feasible if the TELOS-feasibility score was ≥3) (42). The 5

226 questions were answered by the researchers on the basis of the data from two surveys about

227 assessment of malnutrition (43) and sarcopenia (17) in clinical practice across European

228 countries.

229 **5. Covariate data collection:** Clinical and demographic data were collected during annual

230 interviews and phone calls and were used as covariates. Number of concomitant diseases and

231 drugs taken were recorded. The Mini-Nutritional State Examination (MMSE) (maximum

232 score 30 points) was used to assess cognitive status (44). Instrumental activities of daily

233 living (IADL) (maximum score 8 points) were assessed (45). Sarcopenia was defined

234 according to the EWGSOP2, by a low grip strength and low muscle mass. If low physical

235 performance was also present, it was considered "severe sarcopenia" (14). Sarcopenia was

236 measured as recommended by the EWGSOP2 (14) and ESCEO (39) (see above). Diagnosis of

237 sarcopenia was considered as a dichotomous variable (yes/no) and severity grading of

238 sarcopenia was not assessed in our study for purpose of analysis, i.e., individuals with

239 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.

6. 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.

265 The performance indicators that determine the diagnostic properties of an assessment method

266 were calculated for the GLIM criteria and the 7 pragmatic approaches: sensitivity, specificity,

267 positive predictive value (PPV), negative predictive value (NPV), and area under the ROC

268 curve (AUC). An assessment method was considered to have good performance indicators if

269 sensitivity and specificity>80%; fair, if sensitivity or specificity<80% but both values>50%;

270 and poor, if sensitivity or specificity<50% (49)(50)(51). Coherence between GLIM criteria

271 and the 7 pragmatic approaches was reported with the Cohen-kappa coefficient (overall

272 concordance rate). Cohen-kappa (k) values between 0.81 and 1 were considered indicative of

273 almost perfect agreement, 0.6-0.8 indicates strong agreement, 0.4-0.6 indicates moderate

274 agreement, 0.20 to 0.4 indicates low agreement, between 0 and 0.20 indicates very slight

275 agreement and less than 0, indicates disagreement (49)(52). The 5% critical level was

276 considered as statistically significant. SPSS Statistics 24 (IBM Corporation, Armonk, NY,

277 USA) software package was used for data analysis.

7. Ethical statements

279 National and international research ethics guidelines were followed (53), including the

280 Deontological Code of Ethics, 1964 Declaration of Helsinki and its later amendments. Data

281 were entered and treated in accordance with the provisions of the applicable data protection

282 law in Belgium and the General Data Protection Regulation (GDPR) (EU) nº 2016/679 of the

283 European Parliament and Council, dated the 27 April of 2016, which entered into force last 25

284 May 2018. Liège University Ethics Committee's approval was obtained (ref. 2012/277) and

285 all subjects signed the informed consent.

286

RESULTS

288 From the 534 total participants of the SarcoPhAge cohort at baseline, the blood samples

289 needed to assess inflammation and calculate the GLIM criteria were available for 411 (77%)

290 individuals. From them, 373 individuals (69.8%) had data for the outcome "death" available

291 during the 5-year follow-up, and 38 were unavailable by phone or postal survey becoming

292 impossible to get to know about their living status, therefore, they were considered as lost

293 during the follow-up. These 373 individuals (73.07±5.96 years, 56% women) have been

294 considered the study sample (**Figure 1**).

295 **Table 1** shows the clinical characteristics of the sample at baseline. Malnutrition according to

296 the GLIM criteria was present in 91 (24.4%) individuals at baseline and it ranged from 52

297 (13.9%) individuals according to the GLIM criteria without muscle mass, to 78 (20.9%)

298 individuals according to the GLIM criteria with Ishii's score chart when applying the 7

299 pragmatic approaches.

300 **Table 2** shows the 5-year mortality risk for subjects with baseline malnutrition according to

301 the GLIM criteria and the 7 pragmatic approaches. Subjects that met the GLIM criteria had a

302 significant increase in mortality risk, HR: 3.78 (95% Confidence Interval (CI): 2.19-6.53), and

303 that increase was consistent in the adjusted model for age, sex, number of concomitant

304 diseases, number of drugs, level of physical activity and cognitive status as covariates: HR

305 3.38 (95% CI: 1.89-6.04). Subjects that met any of the 7 pragmatic approaches had also a

306 significant increased risk of mortality both in crude and adjusted model. In the adjusted

307 model, the HR ranged between the lowest HR obtained by Goodman grid HR: 2.72 (95% CI

308 1.51-4.91) and the highest obtained by Ishii's score chart HR: 3.94 (95% CI 2.14-7.24).

309 The performance indicators of the 7 pragmatic approaches of the GLIM criteria compared to

310 the original GLIM criteria as the gold standard are showed in **Table 3**. The lowest sensitivity

311 was obtained by the GLIM criteria without a reduced muscle mass [sensitivity= 57.14 (95%

312 CI 46.34 to 67.47)] and the highest by the GLIM criteria with Ishii's score chart [sensitivity=

313 71.43 (95% CI 61.00 to 80.41)], which is coherent with the lowest and the highest prevalence

314 of malnutrition obtained when applying these two approaches, respectively. All of the 7

315 approaches obtained a specificity ≥95%, which ranged from specificity= 95.39 (95% CI 92.25

316 to 97.52) obtained by the GLIM criteria with Ishii's score chart to specificity= 99.30 (98.70 to

317 99.91) obtained by the GLIM criteria without a reduced muscle mass.

318 All the 7 approaches obtained a high PPV, which ranged from the PPV= 83.33 (95% CI 74.35

319 to 89.62) obtained by the GLIM criteria with Ishii's score chart to PPV= 96.30 (95% CI 86.60

320 to 99.05) obtained by the GLIM criteria without a reduced muscle mass. The 7 approaches

321 also obtained a high NPV, with ranged from NPV= 87.85(95%CI 85.08 to 90.17) obtained by

322 the GLIM criteria without a reduced muscle mass and NPV= 91.19 (95% CI 88.19 to 93.48)

323 by Ishii's score chart. Therefore, all the 7 approached showed fair diagnostic performance

324 indicators.

325 The AUC was ≥0.7 for all the approaches (**Figure 2**), ranged from AUC= 0.654 (95%CI

326 0.592 to 0.716) obtained by the GLIM criteria with Yu's formula to AUC= 0.760 (95%CI

327 0.706 to 0.815) obtained by the GLIM criteria with calf circumference. Ishii's score chart had

328 the highest sensitivity (71.4%), NPV (91.19%), and an AUC (0.735).

329 The concordance between the GLIM criteria as gold standard and the 7 pragmatic approaches

330 and the concordance among all of them is showed in **Table 4**. A strong concordance has been

331 found between the original GLIM criteria and the 7 approaches, meaning that both identified

332 almost the same individuals .The values of Cohen kappa coefficient ranged from k= 0.667

333 (0.617 to 0.715, strong concordance) between the GLIM criteria and the GLIM criteria with

15

334   Goodman's grid to k= 0.724 (0.678 to 0.769, strong concordance) between the GLIM criteria

335   and the GLIM criteria with calf-circumference.

336   The results obtained in the TELOS-feasibility assessment are showed in **Table 5**. The GLIM

337   criteria showed a TELOS-feasibility score = 3 and the 7 pragmatic approaches obtained

338   TELOS-feasibility scores ranging from 6 to 7.

339

DISCUSSION

341 Our study showed that the GLIM criteria and the 7 pragmatic approaches predicted three- to

342 four-fold mortality in older community-dwelling population during a 5-year follow-up.

343 Moreover, the pragmatic approaches had correct performance indicators, and were feasible.

344 The prevalence of malnutrition with the original GLIM criteria was 24.4%, while with the

345 pragmatic approaches were 20.9% to 13.9%, which might underestimate prevalence,

346 particularly for the approach "GLIM criteria without a reduced muscle mass", which was the

347 less accurate and less associated with mortality. However, it is important to highlight that,

348 with this exception, all of them had excellent prognosis capability for mortality, ensured an

349 accurate diagnosis, predicted mortality, and can be implemented in clinical practice.

350 The scientific community has faced the challenge of applying the consensus-based GLIM

351 criteria to predict mortality. Contreras et al., (54) applied the GLIM criteria with handgrip

352 strength and their results found an Odds Ratio of 2.72, (CI 1.37-5.40) to predict 6-month

353 mortality in hospitalized advanced cancer patients (54). Sanz-Paris et al., applied the GLIM

354 criteria with calf and mid-arm circumference in older patients with diabetes mellitus and they

355 found that having severe malnutrition at baseline doubled the risk of mortality during the 8-

356 year follow-up (24).

357 Our study might have an impact towards the widespread diffusion of the new GLIM criteria

358 for three reasons; first, our study showed that the GLIM criteria are capable to predict

359 mortality, validated the approaches proposed by the GLIM in the original publication, and

360 showed that the 7 pragmatic approaches were feasible. Importantly, the use of the pragmatic

361 approaches did not have any negative impact in the quality of the diagnosis compared to the

362 original GLIM criteria. Second, a call action to solve the gap between research and clinical

363 practice and to validate pragmatic approaches had been already pointed out by the GLIM,

17

364 ESPEN, and EuGMS (55). This validation study was needed, as despite of the support of the

365 ESPEN and EuGMS to the new criteria, and the interest that the new definition has aroused

366 among the European geriatric societies, there are still no national European guidelines that

367 recommend the GLIM criteria (43). The pitfall of measuring muscle mass (16), the lack of the

368 technical devices to measure it in most of clinical settings (17)(43), and the lack of

369 reimbursement of that procedure had been pointed out as a challenge, i.e., by the Spanish

370 Society of Physical Medicine and Rehabilitation (56).

371 The pragmatic approaches to be included as surrogates of muscle mass and their thresholds

372 were chosen on the basis of three requirements: First, the pragmatic approach had to be

373 applicable in settings with limited resources (from a technical, economical, knowledge, effort,

374 and time point of view); second, they had to be evidence-based, externally validated in other

375 cohorts apart of SarcoPhAge, and finally, the data had to be available in our database at

376 baseline for the post-hoc analysis. Wide evidence was found for calf-circumference and for its

377 threshold <31cm (31)(57)(58), and that was our rationale to choose them. The lowest quartile

378 for calf-circumference in our sample was calculated and it is 32.5 cm, which is quite close to

379 the <31 cm threshold from MNA test reference and does not modified substantially the

380 results, so, the threshold already acknowledged as a reference was used for the analysis.

381 About mid-arm circumference, we were actually interested in including upper arm, in order to

382 avoid the eventual biases of the use of lower limbs, where the frequent occurrence of edema

383 might limit its use in acute process, cardiorespiratory diseases, or immobilized patients,

384 among others. Moreover, upper arm is usually more accessible during physical examination

385 and does not require an extra time for each outpatient visit, i.e. in outpatients' clinics.

386 However, to authors' knowledge, mid-arm circumference in older people lacks of

387 standardized value, therefore, the lowest quartile (<21cm value) was calculated for our

388 sample. This value in SarcoPhAge might be a reference for further research and clinical use.

389 It is important to highlight that muscle depletion and sarcopenia are different entities

390 (2)(15)(59). Muscle depletion or reduced muscle mass is one of the phenotypic criteria for the

391 GLIM, but it is not the same as sarcopenia, which necessarily involves the loss of function.

392 According to EWGSOP2, low strength (e.g. handgrip) indicates probable sarcopenia, when

393 combined with reduced muscle mass sarcopenia is confirmed, and when function is low (e.g.

394 gait speed) severe sarcopenia is present (14). Although sarcopenia does not use inflammation

395 as a defining criterion, inflammation is often linked to (and causative of) sarcopenia (2)(60).

396 The difference between these two concepts was depicted in the ESPEN guidelines on

397 definition and terminology of clinical nutrition, which includes a conceptual tree of

398 malnutrition and nutrition-related diseases, from the basic definition of malnutrition to

399 aetiology-based diagnoses (60). Regarding the longitudinal relationships between the two

400 diseases, malnutrition according to GLIM criteria at baseline has been associated to a four-

401 fold higher risk of the onset of sarcopenia in the SarcoPhAge study during a 4-year follow-up

402 in a recent publication of our research group (1). However, further research is needed on the

403 association between sarcopenia at baseline and the onset of malnutrition according to GLIM

404 criteria during a longitudinal follow-up. This was planned as one of the aims of the study, but

405 has not been conducted yet due to budget limitations. A recent retrospective study in patients

406 from 18 hospitals in Canada explored the diagnostic performance indicators of several

407 combinations of the phenotypic and etiologic criteria, and also including fewer or higher

408 number of criterion and used the subjective global assessment (SGA) as gold standard.

409 Applying all criteria that compose the GLIM definition together, against SGA, obtained a

410 sensitivity of 61.3%; other possible combinations with fewer number of criteria showed much

411 lower sensitivity, e.g., the combination of weight loss AND high CRP had the highest

412 sensitivity (46.33%) with a specificity of 93.02% (PPV: 84.54%; NPV: 67.80%), and the

413 combination of low BMI AND low intake had much lower sensitivity (15.54%) with the

19

414 highest specificity (98.84%). Authors concluded that applying a limited number of criterion

415 might lead to missing out a high percentage of malnourished patients, and therefore,

416 underdiagnose and undertreat a reversible disease (61). These results are aligned with the

417 conclusions of our study, where the 6 pragmatic approaches that included a substitute of

418 muscle mass had higher sensitivity and better diagnostic performance indicators than the

419 simply omission of muscle mass within the criteria. Likewise, the EAMA 9+ study is an

420 ongoing European collaborative project aimed on assessing nutrition-related diseases in acute

421 clinical healthcare settings; the protocol of the study has been published an includes the

422 assessment of malnutrition according to GLIM criteria with handgrip strength and calf

423 circumference (62).

424 A strength of our study is the use of mortality as main outcome, as it is the most robust health

425 adverse consequence. Moreover, the study provides a wide range of solutions for those

426 clinicians that would like to assess their patients' nutritional status with updated tools in order

427 to provide best quality of care (43). Another strength of our study is the inclusion of a

428 feasibility score. Despite available data about the future prevalence of sarcopenia in Europe

429 (63) and the health economic burden of sarcopenia (64), to authors' knowledge studies about

430 feasibility of health interventions are scarce (42)(65) and no feasibility study about the

431 assessment of nutrition-related diseases in clinical practice exists. Feasibility studies might

432 provide solid and objective indicators to guide the implementation of diagnostic and

433 therapeutic interventions (65).

434 Two different types of limitations should be acknowledged; one is derived from the post-hoc

435 nature of our study. First, we were unable to include SARC-F among the pragmatic

436 approaches. The reason is that SARC-F was published in 2013, after the date of baseline

437 assessment of the SarcoPhAge cohort. Despite SARC-F having been administered along the

438 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

464 screening step could be considered as a limitation, this issue does not discriminate the interest

465 of the study, which provides new evidence about the comparison of different pragmatic ways

466 to calculate and define loss of muscle mass. The calculation of the severity grading was also

467 not possible due to the use of the modified threshold for weight loss; to authors' knowledge,

468 only the study from Allard et al., has assessed severity of malnutrition according to the GLIM

469 (61), and exploring severity grading could be a challenging topic for further research.

470 The other type of limitations of our study is related to the study cohort design. The inclusion

471 of general community-dwelling older people might involve a selection bias that has been

472 previously reported in cohorts of community-dwelling older people (68) and in the

473 SarcoPhAge study (1). The characteristics of voluntary older participants (motivation,

474 involvement in self-care management in musculo-skeletal health, etc.) might differ from those

475 who refused to get involved in a research study. Moreover, volunteers recruited were

476 relatively young at baseline, able to walk, without cognitive impairments, and their health

477 status might be better than the general Belgian population of the same age. These eventual

478 biases could have affected the prevalence of malnutrition in our sample, which could be

479 higher in the general older population. The relatively young age and stable overall status is

480 also a strength of the study, as the findings might have higher external validity for general

481 population. Finally, the diseases and the drugs taken by the participants were not listed and

482 this has to be acknowledged as a limitation of our work. However, the number of drugs and

483 number of diseases were recorded in absolute numbers, and they were used as confounders for

484 the analysis.

485 The overall study was conceived to bridge the gap between research and clinical practice and

486 to provide evidence-based solutions for current unmet needs in clinical practice ("Action-

487 research philosophy", "from bedside to bench, to bedside again") (25). Our study might be

488 helpful to better align the interests of the National scientific societies with the interest of the

489 largest societies of clinical nutrition (ESPEN, SSCWD, etc.), EuGMS, etc., as they might be

490 able to endorse the GLIM criteria by now, as they have been shown their predictive capacity

491 for mortality, and there are feasible options available that could improve nutritional care.

492 **Conclusions:** Our study provided 7 pragmatic approaches of the GLIM criteria which

493 predicted three- to four-fold mortality during a 5-year follow-up, showed adequate

494 performance indicators, almost-perfect or strong concordances with the original ones, and

495 were feasible. Clinicians would be free to decide among a wide range of GLIM pragmatic

496 approaches that predict mortality, ensure an accurate diagnosis, and are feasible in clinical

497 settings.

498

499   **Highlights**

500   GLIM and the 7 pragmatic approaches to define muscle loss predicted three- to four-fold

501   mortality during a 5-year follow-up.

502   The prevalence of malnutrition with GLIM criteria was 24.4% and ranged from 13.9% to

503   20.9% using the 7 approaches.

504   The 7 approaches ensured an accurate diagnosis, and were feasible in clinical settings.

505   The 7 approaches might be a step forward to improve diagnosis of malnutrition and

506   nutritional care in clinical settings.

507

508 **Competing interest statement**

509 All authors declare they do not have any financial and personal relationships with other

510 people or organizations that could inappropriately influence their work.

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514

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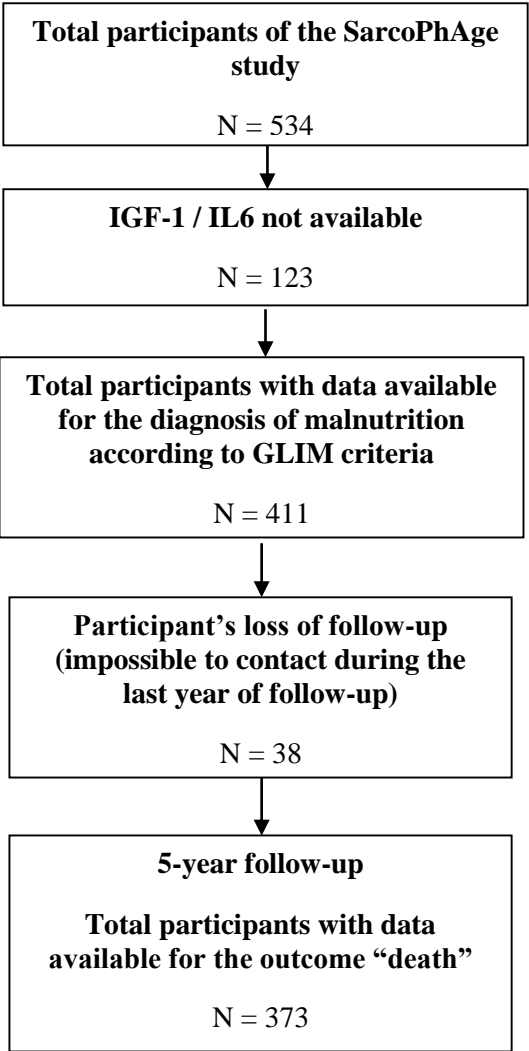557   Apr 22;122:89–90.

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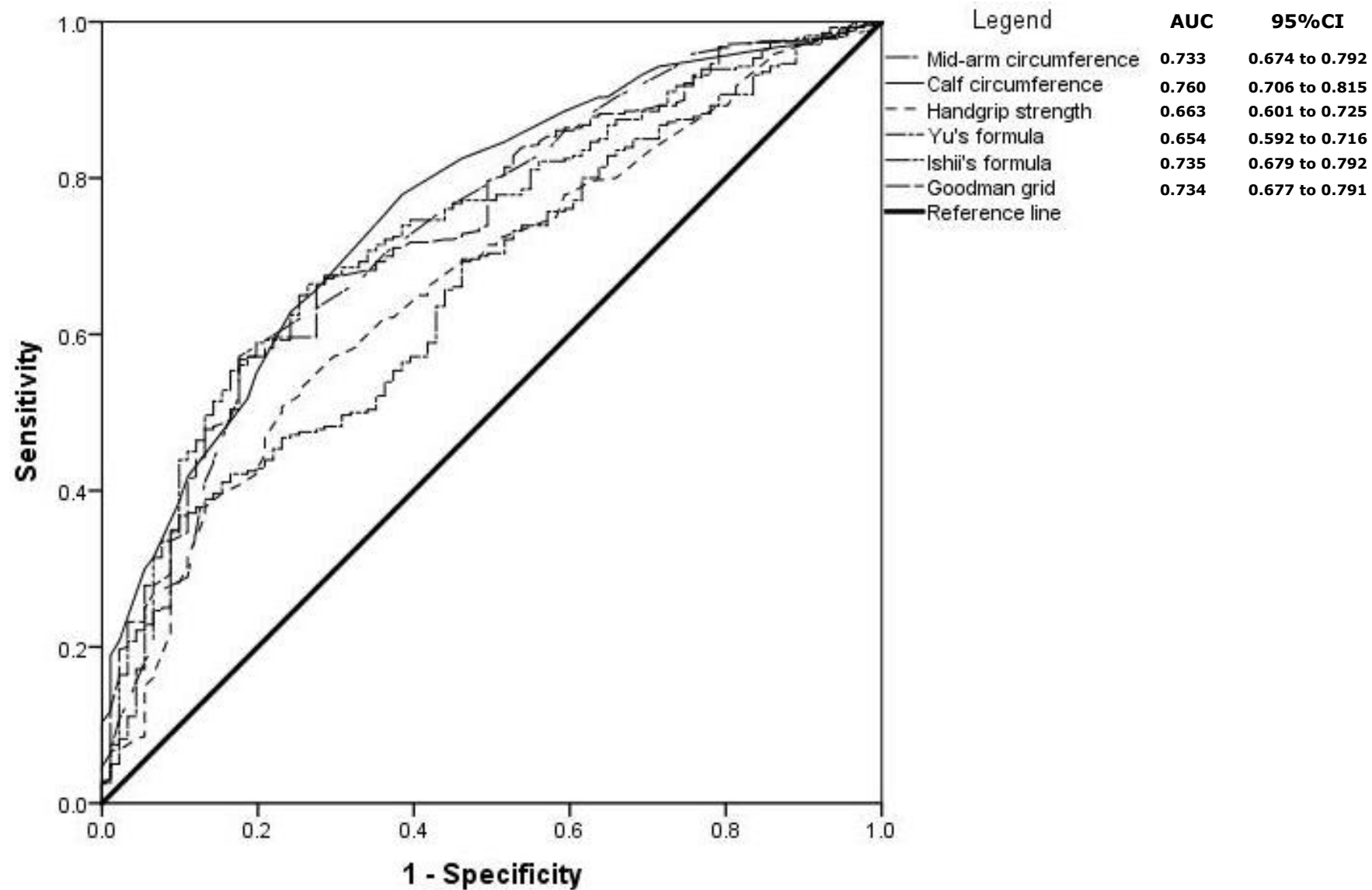
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686

Figure 1

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

```
┌─────────────────────────────────────┐
│  Total participants of the SarcoPhAge│
│                study                 │
│                                      │
│              N = 534                 │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│       IGF-1 / IL6 not available      │
│                                      │
│              N = 123                 │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│  Total participants with data available │
│   for the diagnosis of malnutrition  │
│      according to GLIM criteria      │
│                                      │
│              N = 411                 │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│     Participant's loss of follow-up  │
│   (impossible to contact during the  │
│        last year of follow-up)       │
│                                      │
│              N = 38                  │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│            5-year follow-up          │
│                                      │
│    Total participants with data      │
│  available for the outcome "death"   │
│                                      │
│              N = 373                 │
└─────────────────────────────────────┘
```

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

Legend	AUC	95%CI
Mid-arm circumference	0.733	0.674 to 0.792
Calf circumference	0.760	0.706 to 0.815
Handgrip strength	0.663	0.601 to 0.725
Yu's formula	0.654	0.592 to 0.716
Ishii's formula	0.735	0.679 to 0.792
Goodman grid	0.734	0.677 to 0.791
Reference line		

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 N= 373	Malnutrition according to the GLIM criteria				
		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 N= 373	Malnutrition according to GLIM criteria without a reduced muscle mass				
		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 N= 373	Malnutrition according to GLIM criteria with calf circumference				
		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 N= 373	Malnutrition according to GLIM criteria with handgrip strength				
		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 N= 373	Malnutrition according to GLIM criteria with Ishii's score chart				
		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 N= 373	Malnutrition according to GLIM criteria with mid-arm circumference				
		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 N= 373	Malnutrition according to GLIM criteria with Yu's formula				
		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 N= 373	Malnutrition according to GLIM Criteria with Goodman grid				
		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)

* Because survival data were available, we applied the COX proportion hazards model giving the hazard ration (HR) and 95% confidence interval (CI).

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.

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.

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

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 hour?	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.

1 **Prediction of 5-year mortality risk by malnutrition according to the GLIM format using**

2 **seven pragmatic approaches to define the criterion of loss of muscle mass**

3 **Abstract**

4 **Objectives:** To assess the association between baseline malnutrition according to the GLIM

5 format, using seven pragmatic approaches to define the criterion of loss of muscle mass, with

6 mortality in the SarcoPhAge (*Sarco*penia and *Ph*ysical Impairment with advancing *Age*) study

7 during a 5-year follow-up. Secondarily, to calculate diagnostic performance indicators,

8 concordance, and feasibility of these 7 pragmatic approaches compared to the original GLIM

9 criteria.

10 **Methods:** Post-hoc analysis of the SarcoPhAge cohort, which included 534 community-

11 dwelling volunteers ≥65-year-old, followed-up from 2013 to 2019. Baseline malnutrition was

12 defined by GLIM criteria and 7 approaches: 1) Omission of a reduced muscle mass as a

13 criterion; 2) Substitution for handgrip strength, 3) Calf-circumference, 4) Mid-arm

14 circumference, 5) Goodman's grid, 6) Ishii's score chart, and 7) Yu's formula. The

15 association between malnutrition (according to GLIM criteria and the 7 approaches) and

16 mortality was assessed by Cox-regressions. Sensitivity, Specificity, Positive (PPV), Negative

17 (NPV) predictive values, area under the curve (AUC), Cohen-kappa coefficient, and TELOS-

18 feasibility score were calculated.

19 **Results:** Data to calculate GLIM criteria were available for 373 subjects (73.07±5.96 years,

20 56% women). Prevalence of malnutrition with GLIM criteria was 24.4% (ranged from 13.9%

21 to 20.9% with the 7 approaches). GLIM criteria showed a HR=3.38 (1.89-6.09) to predict

22 mortality during the 5-year follow-up, which ranged from HR=2.72 (1.51-4.91) to 3.94 (2.14-

23 7.24) with the 7 approaches. All 7 approaches were feasible (TELOS≥3), showed

24 sensitivity≥65%, specificity≥95.4%, PPV≥85%, NPV≥88%, AUC≥0.7 and had almost-

25 perfect/strong concordance (k≥0.7) with the original GLIM criteria.

26 **Conclusions:** GLIM criteria and the 7 approaches predicted three- to four-fold mortality, all

27 ensured an accurate diagnosis, and were feasible in clinical settings.

28 **Keywords:** Malnutrition; GLIM; Calf-circumference; Ishii; mortality; SarcoPhAge.

29

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)(5)(6)(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 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

3

54 reduced muscle mass] AND at least one etiologic criterion (reduced food intake or

55 assimilation and disease burden or inflammatory conditions) (10).

56 Muscle mass became part of the GLIM criteria because muscle structure and function depend

57 on nutrition due to the balance between protein synthesis and degradation (12) and because it

58 has been shown to be an independent factor of mortality (13)(14). Magnetic resonance

59 imaging (MRI), dual energy x-ray assessment (DXA), and bioimpedance analysis (BIA)

60 provide moderate to high quality data about muscle structure and are the recommended

61 techniques to measure muscle mass (9)(10)(14). However, these techniques are not

62 standardized yet, have limited access for research, and are not feasible in most of healthcare

63 settings (15)(16)(17). Aware of the challenge that the measurement of muscle mass involves

64 for the widespread use of the GLIM criteria, ==GLIM proposed pragmatic approaches:==

65 ==Substituting a phenotypic criterion like calf-circumference or mid-arm circumference, or==

66 ==handgrip strength for muscle mass (10).==

67 Muscle mass is also a component of sarcopenia as defined by the latest consensus published

68 by the European Working Group on Sarcopenia in Older People (EWGSOP), the revised

69 European consensus on definition and diagnosis (EWGSOP2) (14). By sharing muscle mass,

70 the new definitions of malnutrition and sarcopenia were harmonized, in order to gain

71 knowledge and develop shared diagnostic and therapeutic interventions that might benefit the

72 two diseases (18). Some screening methods for sarcopenia have shown good correlation with

73 muscle mass (19): e.g. Ishii's score chart (20), Yu's formula (21), and Goodman's grid (22),

74 and the equipment required to administer them (measuring tape, weighbridge, or handgrip

75 dynamometer) is inexpensive, available in less resourced healthcare settings.

76 The capacity of the GLIM criteria to predict mortality has been recently shown in hospitalized

77 patients with cancer (23) and in older patients with diabetes mellitus (24); however, the

78 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.

METHODS

98   The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

99   Statement was followed (26).

1. Population

101   Post-hoc analysis of a cohort study, the SarcoPhAge study, which aimed on assessing health

102   and functional adverse consequences of sarcopenia in community-dwelling older adults

103   during a 5 years follow-up. The study was conducted in Belgium and included 534 older

104   volunteers at baseline, which were annually followed-up from June 2013 to September 2019.

105   A complete protocol of the SarcoPhAge study is available (1)(27)(28).

106   **Inclusion criteria:** Community-dwelling volunteers ≥65 years old were included in the

107   SarcoPhAge cohort, with no selection criteria related to health or demographic characteristics.

108   **Exclusion criteria:** Amputated limb or body mass index (BMI) ≥50 kg/m². For this post-hoc

109   analysis in the SarcoPhAge cohort, two additional eligibility criteria were applied: to have the

110   variables needed to calculate the GLIM criteria available at baseline and the data of death

111   available during the 5-year follow-up. Data collection and procedures have been previously

112   described in detail (1)(28)(29).

113   **2. Diagnosis of malnutrition according to GLIM criteria:** Malnutrition according to the

114   GLIM criteria is composed by a 3-step diagnostic structure (10): screening, diagnosis, and

115   severity grading. For the purpose of analysis, diagnosis of malnutrition was applied to all

116   study sample at baseline and considered as a dichotomous variable (yes/no). Therefore, the

117   first screening step and the severity grading step proposed by the GLIM were not applied in

118   the study. The rationale for this decision was 1) because we wanted to include the largest

119   number as possible of participants in the analyses; and 2) because the assessment, at baseline,

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).

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

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:

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)(36)(37).

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).

3.4. **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,

$0.62 \times (\text{age} - 64) - 3.09 \times (\text{handgrip strength} - 50) - 4.64 \times (\text{calf-circumference} - 42)$;

score in women, $0.80 \times (\text{age} - 64) - 5.09 \times (\text{handgrip strength} - 34) - 3.28 \times (\text{calf-}$

circumference $- 42)$. Sex-specific thresholds used were ≥ 105 for men and ≥ 120 for

women (19)(20).

3.5. **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)

9

190 and reported by Frisancho et al., (40). The lowest quartile (a value <21 cm) was computed

191 for SarcoPhAge and used as threshold (24).

3.6. **GLIM criteria with Yu's formula:** It requires the measurement of weight and height,

193 and BMI. The appendicular skeletal muscle mass prediction equation was: 10.05+0.35

194 (weight) - 0.62 (BMI)-0.02 (age) +5.10 (if male). A value below the 20th percentile was

195 computed for SarcoPhAge and used as threshold (19).

3.7. **GLIM criteria with Goodman Grid** (22) : Goodman grids provides the probability

197 (%) of low muscle mass. It is constructed separately for men and women by using age and

198 sex-specific BMI. A threshold ≥70% in men and ≥80% in women was considered as

199 indicative of low muscle mass (22), as previously reported in SarcoPhAge (19).

4. Main outcome measure: Deaths during the 5-year follow-up in the SarcoPhAge study

201 according to the presence of malnutrition at baseline. Data for the survival curve were

202 collected annually by direct interview or assessed by medical records or phone calls with

203 relatives and caregivers if the participant did not attend the annual visit. **Secondary outcome**

measures were: 1) Diagnostic performance indicators [sensitivity, specificity, positive

205 predictive value (PPV), negative predictive value (NPV), and area under the ROC curve

206 (AUC)], and concordance (Cohen-kappa coefficient) of the 7 pragmatic approaches of GLIM

207 criteria compared to the original GLIM criteria. 2) Feasibility of the GLIM criteria and the 7

208 pragmatic approaches, measured by the Technological, Economical, Legal, Operational,

209 Schedule (TELOS)-feasibility score.

210 Feasibility was defined as "the state or degree of being easily or conveniently done (41)" and

211 explored by the TELOS-feasibility score, which assess the potential of implementation of new

212 systems. This model is used in Engineering and has been also applied into Medicine (42).

213 Five areas were assessed by polar answers (yes/no): Technological ("Is the tool available in

214 the clinical setting? Is staff trained to implement the new method?" Yes, if a training

215 infrastructure is available in the clinical setting), Economic ("Is the cost of training

216 acceptable? Is the training period less than 1 hour?" Yes, if no additional cost in terms of

217 money are needed, and less than 1 hour of training period in terms of time), Legal ("Does the

218 assessment conflict with legal requirements?"), Operational ("Does the assessment method

219 solve a clinical problem? Is muscle assessment required in clinical practice?" Yes, if

220 assessment of malnutrition is considered as relevant in clinical practice), and Schedule ("Does

221 the procedure take less time than the current standard method of measurement?" Yes, if the

222 procedure takes less than the time needed to measure muscle mass by the GLIM criteria). A

223 positive answer scores 1 point in the TELOS-feasibility score, the legal area is not included in

224 the sum up of the score, and a "no" in that area is mandatory to continue the study.

225 Interventions were considered feasible if the TELOS-feasibility score was ≥ 3) (42). The 5

226 questions were answered by the researchers on the basis of the data from two surveys about

227 assessment of malnutrition (43) and sarcopenia (17) in clinical practice across European

228 countries.

229 **5. Covariate data collection:** Clinical and demographic data were collected during annual

230 interviews and phone calls and were used as covariates. Number of concomitant diseases and

231 drugs taken were recorded. The Mini-Nutritional State Examination (MMSE) (maximum

232 score 30 points) was used to assess cognitive status (44). Instrumental activities of daily

233 living (IADL) (maximum score 8 points) were assessed (45). Sarcopenia was defined

234 according to the EWGSOP2, by a low grip strength and low muscle mass. If low physical

235 performance was also present, it was considered "severe sarcopenia" (14). Sarcopenia was

236 measured as recommended by the EWGSOP2 (14) and ESCEO (39) (see above). Diagnosis of

237 sarcopenia was considered as a dichotomous variable (yes/no) and severity grading of

238 sarcopenia was not assessed in our study for purpose of analysis, i.e., individuals with

239 sarcopenia or severe sarcopenia computed equally. The Minnesota Leisure Time Activity

240 Questionnaire was used to quantify the self-reported time spent in different physical activities

241 in the past last 7 days and its sex-specific thresholds were followed (46). The Short-form (SF)

242 36 Physical Component Summary (PCS) score, the SF-36 Mental Health Component

243 Summary (MCS) score (maximum 100 points) (47), and the EuroQol 5D [(ranged from 0 (the

244 worst possible health status) to 1 (the best possible health status)] (48) were administered at

245 baseline to assess quality of life.

246 **6. Statistical method:** Absolute and relative (%) frequencies were used to express qualitative

247 variables; mean ± standard deviation was used to express quantitative variables following a

248 Gaussian distribution; median (percentile 25 – percentile 75) were used to express

249 quantitative variables following a skewed distribution. The normality of the variables was

250 checked by exploring the difference between the mean and the median values, the histogram,

251 the quantile–quantile plot, and the Shapiro–Wilk test.

252 The characteristics of all subjects were evaluated at baseline. The number of participants with

253 malnutrition diagnosed according to either GLIM criteria or the 7 pragmatic approaches were

254 measured. Characteristics of subjects diagnosed with malnutrition with either GLIM criteria

255 or the 7 pragmatic approaches were compared against subjects with no malnutrition through a

256 logistic regression. Sex was introduced as a covariate in the regression for well-known sex-

257 specific variables (muscle strength, fat-free mass, FFMI, ALMI, and gait speed).

258 The relationship between malnutrition and risk of mortality was explored. The Cox

259 proportional hazards model, giving the hazard ratio (HR) and 95% confidence interval (CI)

260 was applied for mortality. Crude and adjusted HR were computed for two models: in the first

261 multivariate model, age and sex were included as confounders; in the second model, the age,

262 sex, number of concomitant diseases, number of drugs, physical activity level and cognitive

263 status were included as confounders, due to the known effect of these variables in muscle

264 mass.

265 The performance indicators that determine the diagnostic properties of an assessment method

266 were calculated for the GLIM criteria and the 7 pragmatic approaches: sensitivity, specificity,

267 positive predictive value (PPV), negative predictive value (NPV), and area under the ROC

268 curve (AUC). An assessment method was considered to have good performance indicators if

269 sensitivity and specificity>80%; fair, if sensitivity or specificity<80% but both values>50%;

270 and poor, if sensitivity or specificity<50% (49)(50)(51). Coherence between GLIM criteria

271 and the 7 pragmatic approaches was reported with the Cohen-kappa coefficient (overall

272 concordance rate). Cohen-kappa (k) values between 0.81 and 1 were considered indicative of

273 almost perfect agreement, 0.6-0.8 indicates strong agreement, 0.4-0.6 indicates moderate

274 agreement, 0.20 to 0.4 indicates low agreement, between 0 and 0.20 indicates very slight

275 agreement and less than 0, indicates disagreement (49)(52). The 5% critical level was

276 considered as statistically significant. SPSS Statistics 24 (IBM Corporation, Armonk, NY,

277 USA) software package was used for data analysis.

7. Ethical statements

279 National and international research ethics guidelines were followed (53), including the

280 Deontological Code of Ethics, 1964 Declaration of Helsinki and its later amendments. Data

281 were entered and treated in accordance with the provisions of the applicable data protection

282 law in Belgium and the General Data Protection Regulation (GDPR) (EU) nº 2016/679 of the

283 European Parliament and Council, dated the 27 April of 2016, which entered into force last 25

284 May 2018. Liège University Ethics Committee's approval was obtained (ref. 2012/277) and

285 all subjects signed the informed consent.

286

RESULTS

288   From the 534 total participants of the SarcoPhAge cohort at baseline, the blood samples

289   needed to assess inflammation and calculate the GLIM criteria were available for 411 (77%)

290   individuals. From them, 373 individuals (69.8%) had data for the outcome "death" available

291   during the 5-year follow-up, and 38 were unavailable by phone or postal survey becoming

292   impossible to get to know about their living status, therefore, they were considered as lost

293   during the follow-up. These 373 individuals (73.07±5.96 years, 56% women) have been

294   considered the study sample (**Figure 1**).

295   **Table 1** shows the clinical characteristics of the sample at baseline. Malnutrition according to

296   the GLIM criteria was present in 91 (24.4%) individuals at baseline and it ranged from 52

297   (13.9%) individuals according to the GLIM criteria without muscle mass, to 78 (20.9%)

298   individuals according to the GLIM criteria with Ishii's score chart when applying the 7

299   pragmatic approaches.

300   **Table 2** shows the 5-year mortality risk for subjects with baseline malnutrition according to

301   the GLIM criteria and the 7 pragmatic approaches. Subjects that met the GLIM criteria had a

302   significant increase in mortality risk, HR: 3.78 (95% Confidence Interval (CI): 2.19-6.53), and

303   that increase was consistent in the adjusted model for age, sex, number of concomitant

304   diseases, number of drugs, level of physical activity and cognitive status as covariates: HR

305   3.38 (95% CI: 1.89-6.04). Subjects that met any of the 7 pragmatic approaches had also a

306   significant increased risk of mortality both in crude and adjusted model. In the adjusted

307   model, the HR ranged between the lowest HR obtained by Goodman grid HR: 2.72 (95% CI

308   1.51-4.91) and the highest obtained by Ishii's score chart HR: 3.94 (95% CI 2.14-7.24).

309   The performance indicators of the 7 pragmatic approaches of the GLIM criteria compared to

310   the original GLIM criteria as the gold standard are showed in **Table 3**. The lowest sensitivity

14

311 was obtained by the GLIM criteria without a reduced muscle mass [sensitivity= 57.14 (95%

312 CI 46.34 to 67.47)] and the highest by the GLIM criteria with Ishii's score chart [sensitivity=

313 71.43 (95% CI 61.00 to 80.41)], which is coherent with the lowest and the highest prevalence

314 of malnutrition obtained when applying these two approaches, respectively. All of the 7

315 approaches obtained a specificity ≥95%, which ranged from specificity= 95.39 (95% CI 92.25

316 to 97.52) obtained by the GLIM criteria with Ishii's score chart to specificity= 99.30 (98.70 to

317 99.91) obtained by the GLIM criteria without a reduced muscle mass.

318 All the 7 approaches obtained a high PPV, which ranged from the PPV= 83.33 (95% CI 74.35

319 to 89.62) obtained by the GLIM criteria with Ishii's score chart to PPV= 96.30 (95% CI 86.60

320 to 99.05) obtained by the GLIM criteria without a reduced muscle mass. The 7 approaches

321 also obtained a high NPV, with ranged from NPV= 87.85(95%CI 85.08 to 90.17) obtained by

322 the GLIM criteria without a reduced muscle mass and NPV= 91.19 (95% CI 88.19 to 93.48)

323 by Ishii's score chart. Therefore, all the 7 approached showed fair diagnostic performance

324 indicators.

325 The AUC was ≥0.7 for all the approaches (**Figure 2**), ranged from AUC= 0.654 (95%CI

326 0.592 to 0.716) obtained by the GLIM criteria with Yu's formula to AUC= 0.760 (95%CI

327 0.706 to 0.815) obtained by the GLIM criteria with calf circumference. Ishii's score chart had

328 the highest sensitivity (71.4%), NPV (91.19%), and an AUC (0.735).

329 The concordance between the GLIM criteria as gold standard and the 7 pragmatic approaches

330 and the concordance among all of them is showed in **Table 4**. A strong concordance has been

331 found between the original GLIM criteria and the 7 approaches, meaning that both identified

332 almost the same individuals .The values of Cohen kappa coefficient ranged from k= 0.667

333 (0.617 to 0.715, strong concordance) between the GLIM criteria and the GLIM criteria with

15

334 Goodman's grid to k= 0.724 (0.678 to 0.769, strong concordance) between the GLIM criteria

335 and the GLIM criteria with calf-circumference.

336 The results obtained in the TELOS-feasibility assessment are showed in **Table 5**. The GLIM

337 criteria showed a TELOS-feasibility score = 3 and the 7 pragmatic approaches obtained

338 TELOS-feasibility scores ranging from 6 to 7.

339

DISCUSSION

341 Our study showed that the GLIM criteria and the 7 pragmatic approaches predicted three- to

342 four-fold mortality in older community-dwelling population during a 5-year follow-up.

343 Moreover, the pragmatic approaches had correct performance indicators, and were feasible.

344 The prevalence of malnutrition with the original GLIM criteria was 24.4%, while with the

345 pragmatic approaches were 20.9% to 13.9%, which might underestimate prevalence,

346 particularly for the approach "GLIM criteria without a reduced muscle mass", which was the

347 less accurate and less associated with mortality. However, it is important to highlight that,

348 with this exception, all of them had excellent prognosis capability for mortality, ensured an

349 accurate diagnosis, predicted mortality, and can be implemented in clinical practice.

350 The scientific community has faced the challenge of applying the consensus-based GLIM

351 criteria to predict mortality. Contreras et al., (54) applied the GLIM criteria with handgrip

352 strength and their results found an Odds Ratio of 2.72, (CI 1.37-5.40) to predict 6-month

353 mortality in hospitalized advanced cancer patients (54). Sanz-Paris et al., applied the GLIM

354 criteria with calf and mid-arm circumference in older patients with diabetes mellitus and they

355 found that having severe malnutrition at baseline doubled the risk of mortality during the 8-

356 year follow-up (24).

357 Our study might have an impact towards the widespread diffusion of the new GLIM criteria

358 for three reasons; first, our study showed that the GLIM criteria are capable to predict

359 mortality, validated the approaches proposed by the GLIM in the original publication, and

360 showed that the 7 pragmatic approaches were feasible. Importantly, the use of the pragmatic

361 approaches did not have any negative impact in the quality of the diagnosis compared to the

362 original GLIM criteria. Second, a call action to solve the gap between research and clinical

363 practice and to validate pragmatic approaches had been already pointed out by the GLIM,

17

364 ESPEN, and EuGMS (55). This validation study was needed, as despite of the support of the

365 ESPEN and EuGMS to the new criteria, and the interest that the new definition has aroused

366 among the European geriatric societies, there are still no national European guidelines that

367 recommend the GLIM criteria (43). The pitfall of measuring muscle mass (16), the lack of the

368 technical devices to measure it in most of clinical settings (17)(43), and the lack of

369 reimbursement of that procedure had been pointed out as a challenge, i.e., by the Spanish

370 Society of Physical Medicine and Rehabilitation (56).

371 The pragmatic approaches to be included as surrogates of muscle mass and their thresholds

372 were chosen on the basis of three requirements: First, the pragmatic approach had to be

373 applicable in settings with limited resources (from a technical, economical, knowledge, effort,

374 and time point of view); second, they had to be evidence-based, externally validated in other

375 cohorts apart of SarcoPhAge, and finally, the data had to be available in our database at

376 baseline for the post-hoc analysis. Wide evidence was found for calf-circumference and for its

377 threshold <31cm (31)(57)(58), and that was our rationale to choose them. The lowest quartile

378 for calf-circumference in our sample was calculated and it is 32.5 cm, which is quite close to

379 the <31 cm threshold from MNA test reference and does not modified substantially the

380 results, so, the threshold already acknowledged as a reference was used for the analysis.

381 About mid-arm circumference, we were actually interested in including upper arm, in order to

382 avoid the eventual biases of the use of lower limbs, where the frequent occurrence of edema

383 might limit its use in acute process, cardiorespiratory diseases, or immobilized patients,

384 among others. Moreover, upper arm is usually more accessible during physical examination

385 and does not require an extra time for each outpatient visit, i.e. in outpatients' clinics.

386 However, to authors' knowledge, mid-arm circumference in older people lacks of

387 standardized value, therefore, the lowest quartile (<21cm value) was calculated for our

388 sample. This value in SarcoPhAge might be a reference for further research and clinical use.

18

389 It is important to highlight that muscle depletion and sarcopenia are different entities

390 (2)(15)(59). Muscle depletion or reduced muscle mass is one of the phenotypic criteria for the

391 GLIM, but it is not the same as sarcopenia, which necessarily involves the loss of function.

392 According to EWGSOP2, low strength (e.g. handgrip) indicates probable sarcopenia, when

393 combined with reduced muscle mass sarcopenia is confirmed, and when function is low (e.g.

394 gait speed) severe sarcopenia is present (14). Although sarcopenia does not use inflammation

395 as a defining criterion, inflammation is often linked to (and causative of) sarcopenia (2)(60).

396 The difference between these two concepts was depicted in the ESPEN guidelines on

397 definition and terminology of clinical nutrition, which includes a conceptual tree of

398 malnutrition and nutrition-related diseases, from the basic definition of malnutrition to

399 aetiology-based diagnoses (60). Regarding the longitudinal relationships between the two

400 diseases, malnutrition according to GLIM criteria at baseline has been associated to a four-

401 fold higher risk of the onset of sarcopenia in the SarcoPhAge study during a 4-year follow-up

402 in a recent publication of our research group (1). However, further research is needed on the

403 association between sarcopenia at baseline and the onset of malnutrition according to GLIM

404 criteria during a longitudinal follow-up. This was planned as one of the aims of the study, but

405 has not been conducted yet due to budget limitations. A recent retrospective study in patients

406 from 18 hospitals in Canada explored the diagnostic performance indicators of several

407 combinations of the phenotypic and etiologic criteria, and also including fewer or higher

408 number of criterion and used the subjective global assessment (SGA) as gold standard.

409 Applying all criteria that compose the GLIM definition together, against SGA, obtained a

410 sensitivity of 61.3%; other possible combinations with fewer number of criteria showed much

411 lower sensitivity, e.g., the combination of weight loss AND high CRP had the highest

412 sensitivity (46.33%) with a specificity of 93.02% (PPV: 84.54%; NPV: 67.80%), and the

413 combination of low BMI AND low intake had much lower sensitivity (15.54%) with the

414 highest specificity (98.84%). Authors concluded that applying a limited number of criterion

415 might lead to missing out a high percentage of malnourished patients, and therefore,

416 underdiagnose and undertreat a reversible disease (61). These results are aligned with the

417 conclusions of our study, where the 6 pragmatic approaches that included a substitute of

418 muscle mass had higher sensitivity and better diagnostic performance indicators than the

419 simply omission of muscle mass within the criteria. Likewise, the EAMA 9+ study is an

420 ongoing European collaborative project aimed on assessing nutrition-related diseases in acute

421 clinical healthcare settings; the protocol of the study has been published an includes the

422 assessment of malnutrition according to GLIM criteria with handgrip strength and calf

423 circumference (62).

424 A strength of our study is the use of mortality as main outcome, as it is the most robust health

425 adverse consequence. Moreover, the study provides a wide range of solutions for those

426 clinicians that would like to assess their patients' nutritional status with updated tools in order

427 to provide best quality of care (43). Another strength of our study is the inclusion of a

428 feasibility score. Despite available data about the future prevalence of sarcopenia in Europe

429 (63) and the health economic burden of sarcopenia (64), to authors' knowledge studies about

430 feasibility of health interventions are scarce (42)(65) and no feasibility study about the

431 assessment of nutrition-related diseases in clinical practice exists. Feasibility studies might

432 provide solid and objective indicators to guide the implementation of diagnostic and

433 therapeutic interventions (65).

434 Two different types of limitations should be acknowledged; one is derived from the post-hoc

435 nature of our study. First, we were unable to include SARC-F among the pragmatic

436 approaches. The reason is that SARC-F was published in 2013, after the date of baseline

437 assessment of the SarcoPhAge cohort. Despite SARC-F having been administered along the

438 follow-up of the cohort (19), unfortunately, there are not enough data to calculate the score at

439 baseline retrospectively in the SarcoPhAge study. This lack of available data also affected the

440 inclusion of SARC-CalF 31 and SARC-CalF 33 (57) in our study, and assessing their

441 prognosis capability and diagnostic properties as substitute of muscle mass for GLIM criteria

442 could be an interesting topic for further research. Second, unintentional weight loss >4.5 kg in

443 the past year was used as a threshold for unintentional weight loss (30), which slightly differs

444 from the amount of weight loss over time recommended by the GLIM (def. >5% in 6 months

445 or >10% beyond). Authors consider that this is a minor issue, as weight loss >4.5 kg in the

446 past year has been shown to be a strong predictor of mortality in the Cardiovascular Health

447 Study, among others (30)(66). Moreover, the other two phenotypic criteria were applied as

448 indicated in the original GLIM criteria, therefore, it is unlikely that the small modification in

449 that criterion causes an impact in the prevalence of malnutrition at baseline in the SarcoPhAge

450 study. A recent survey among specialists in Geriatric Medicine from 14 European countries,

451 showed that unintentional weight loss was the phenotypic criterion most frequently

452 recommended in national guidelines about malnutrition. However, there was not consistency

453 in the relevant time-period for over which to consider weight loss, which varied widely (43);

454 the percentages proposed by GLIM would be an opportunity to harmonize the thresholds to

455 consider a weight loss as clinically relevant. Third, regarding the etiologic criteria, disease

456 burden and food assimilation were not assessed in the study, and it could be considered as a

457 limitation. Finally, all participants in our sample were assessed for malnutrition and the first

458 screening step was omitted for study purposes, in order to include the largest possible sample

459 for the calculation of muscle mass. The direct consequence was that the overall prevalence of

460 malnutrition obtained was larger than the one expected by the GLIM for community-dwelling

461 older people. In fact, it is very likely that the prevalence is, in reality, smaller than 24%, since

462 previous studies (using other tools than the GLIM) indicate that around 5-10 percent of

463 community-dwelling older people are malnourished (67). Although the omission of the first

464 screening step could be considered as a limitation, this issue does not discriminate the interest

465 of the study, which provides new evidence about the comparison of different pragmatic ways

466 to calculate and define loss of muscle mass. The calculation of the severity grading was also

467 not possible due to the use of the modified threshold for weight loss; to authors' knowledge,

468 only the study from Allard et al., has assessed severity of malnutrition according to the GLIM

469 (61), and exploring severity grading could be a challenging topic for further research.

470 The other type of limitations of our study is related to the study cohort design. The inclusion

471 of general community-dwelling older people might involve a selection bias that has been

472 previously reported in cohorts of community-dwelling older people (68) and in the

473 SarcoPhAge study (1). The characteristics of voluntary older participants (motivation,

474 involvement in self-care management in musculo-skeletal health, etc.) might differ from those

475 who refused to get involved in a research study. Moreover, volunteers recruited were

476 relatively young at baseline, able to walk, without cognitive impairments, and their health

477 status might be better than the general Belgian population of the same age. These eventual

478 biases could have affected the prevalence of malnutrition in our sample, which could be

479 higher in the general older population. The relatively young age and stable overall status is

480 also a strength of the study, as the findings might have higher external validity for general

481 population. Finally, the diseases and the drugs taken by the participants were not listed and

482 this has to be acknowledged as a limitation of our work. However, the number of drugs and

483 number of diseases were recorded in absolute numbers, and they were used as confounders for

484 the analysis.

485 The overall study was conceived to bridge the gap between research and clinical practice and

486 to provide evidence-based solutions for current unmet needs in clinical practice ("Action-

487 research philosophy", "from bedside to bench, to bedside again") (25). Our study might be

488 helpful to better align the interests of the National scientific societies with the interest of the

489 largest societies of clinical nutrition (ESPEN, SSCWD, etc.), EuGMS, etc., as they might be

490 able to endorse the GLIM criteria by now, as they have been shown their predictive capacity

491 for mortality, and there are feasible options available that could improve nutritional care.

492 **Conclusions:** Our study provided 7 pragmatic approaches of the GLIM criteria which

493 predicted three- to four-fold mortality during a 5-year follow-up, showed adequate

494 performance indicators, almost-perfect or strong concordances with the original ones, and

495 were feasible. Clinicians would be free to decide among a wide range of GLIM pragmatic

496 approaches that predict mortality, ensure an accurate diagnosis, and are feasible in clinical

497 settings.

498

Highlights

GLIM and the 7 pragmatic approaches to define muscle loss predicted three- to four-fold mortality during a 5-year follow-up.

The prevalence of malnutrition with GLIM criteria was 24.4% and ranged from 13.9% to 20.9% using the 7 approaches.

The 7 approaches ensured an accurate diagnosis, and were feasible in clinical settings.

The 7 approaches might be a step forward to improve diagnosis of malnutrition and nutritional care in clinical settings.

Competing interest statement

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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686

1   <mark>**Prediction of 5-year mortality risk by malnutrition according to the GLIM format**</mark>

2   <mark>**using seven pragmatic approaches to define the criterion of loss of muscle mass**</mark>

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22   and approved the final version of the manuscript.

23   **LIST OF ABREVIATIONS**

24   **ALMI:** Appendicular lean mass index

25   **ASPEN:** American Society for Parenteral and Enteral Nutrition

26   **BIA:** Bioimpedance analysis

27   **DXA:** dual energy X-ray assessment

28   **ESPEN:** European Society of Clinical Nutrition and Metabolism

29   **EuGMS:** European Union Geriatric Medicine Society

30   **EWGSOP2:** Revised European consensus on definition and diagnosis

31   **FFMI:** Fat-free mass index

32   **GLIM:** Global Leadership Initiative on Malnutrition

33   **IADL:** Instrumental activities of daily living

34   **ICD-10:** International Classification of Disease

35   **IGF-1:** Insulin-growth factor 1

36   **IL-6:** Interleukin-6

37   **MMSE:** Mini-Mental State Examination

38   **MNA**: Mini-Nutritional Assessment

39   **MRI:** Magnetic resonance imaging

40   **MSC score:** Mental composite score

41   **PSC** score: Physical composite score

42   **SarcoPhAge:** *Sarco*penia and *Ph*ysical Impairment with advancing Age

43   **SF**: Short Form

44   **SPPB:** Short Physical Performance Battery

Highlights

GLIM and the 7 pragmatic approaches to define muscle loss predicted three- to four-fold mortality during a 5-year follow-up.

The prevalence of malnutrition with GLIM criteria was 24.4% and ranged from 13.9% to 20.9% using the 7 approaches.

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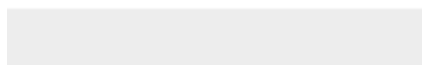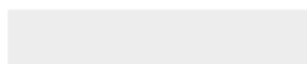
The 7 approaches might be a step forward to improve diagnosis of malnutrition and nutritional care in clinical settings.
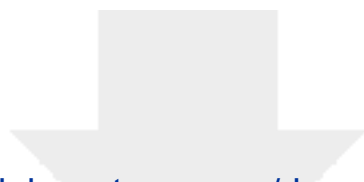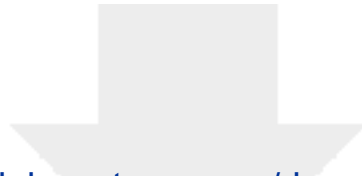
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Credit Authors statement: DSR, ML and CB wrote the manuscript; DSR did literature review; ML, LL, and CB participated in data collection; ML and CB analyzed and interpreted data; JYR, EC, OB, and CB corrected the manuscript. All co-authors read and approved the final version of the manuscript.