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INTRINSIC CAPACITY AND RISK OF DEATH: FOCUS ON THE IMPACT OF USING DIFFERENT DIAGNOSTIC CRITERIA FOR THE NUTRITIONAL DOMAIN

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Abstract

Objective: We aimed to estimate the ability of intrinsic capacity (IC) to predict death in community-dwelling older people using different diagnostic criteria to define the nutritional domain.

Methods: Participants from the Belgian SarcoPhAge cohort were followed from 2013 to the present. Four IC domains were assessed at baseline (data on the sensorial domain were not collected), and considered unsatisfactory below some specific thresholds. The nutritional domain was considered unsatisfactory if baseline malnutrition was present, defined by: 1) MNA-SF ≤11 points; 2) seven versions of the GLIM criteria, varying by the technique used to identify a reduced muscle mass; or 3) the combination of MNA-SF ≤11 points + GLIM criteria. The association between baseline unsatisfactory IC and 9-year mortality was calculated using the odds ratio (OR) adjusted for cofounders.

Results: Among the 534 participants (73.5 ± 6.2 years old; 60.3 % women at baseline), 157 (29.4 %) were dead after 9.3 ± 0.3 years of follow-up. Patients with baseline unsatisfactory IC in the locomotor domain (adjusted OR = 2.31 [95%CI 1.38–3.86]) or psychological domain (adjusted OR = 1.78 [1.12–2.83]) were at higher mortality risk. Regarding malnutrition, unsatisfactory IC in the nutrition domain was strongly associated with a higher mortality risk, whatever the criteria used to identify a reduced muscle mass. The highest association with mortality was found in participants with a baseline unsatisfactory nutritional domain defined by the combination of MNA-SF + GLIM criteria (adjusted OR = 3.27 [95%CI 1.72–6.23]).

Conclusions: Presenting any unsatisfactory IC at baseline was associated with a higher 9-year mortality risk in community-dwelling older people. The sequential incorporation of MNA-SF *and* GLIM criteria as the IC nutritional domain would be helpful to guide public health actions towards healthy ageing

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Malnutrition in adults, Intrinsic capacity, GLIM criteria, GLIS on sarcopenia, SarcoPhAge

1. Introduction

Intrinsic capacity (IC) is a multidimensional construct, defined as "the composite of all the physical and mental capacities of an individual", launched by the World Health Organization (WHO) in the World Report on Ageing and Health in 2016 [1,2]. An unsatisfactory IC is associated to adverse health outcomes and higher mortality-risk [3–5] and has been proposed as outcome indicator of healthy ageing and Public Health actions by the WHO Integrated Care for Older People (ICOPE) Guidelines [6,7]. Joining forces with the United Nations, the WHO has proclaimed the Decade of Healthy Ageing 2021–2030.

Nutrition is one of the five domains which form the IC, as an adequate nutritional status is necessary for an individual to remain in good health [2,3], and its deficits, i.e., malnutrition in adults, is a major health problem, particularly in older people, where it is associated to 7- fold higher mortality-risk [8]. Moreover, malnutrition is reversible, which makes it a good target for person-centered interventions and Public Health actions [9]. Nutritional care is the process which allows to reverse malnutrition's adverse outcomes and "involves five distinct, interrelated phases that should be provided in a systematic sequence", where the first and second phases are malnutrition risk screening and diagnostic assessment, respectively [10]. The Global Leadership Initiative of Malnutrition (GLIM) criteria incorporate the first and second phases of nutritional care, and have been established as the reference operational definition of malnutrition in adults since 2018. Furthermore, efforts are currently underway to obtain a clinically relevant diagnosis code from the WHO International Classification of Diseases (ICD-11) [11–13]. The Global Leadership Initiative of Malnutrition (GLIM) criteria consists in 3-steps: first, malnutrition risk screening by any validated screening tool; second, diagnostic assessment based on phenotypic and etiologic criteria; third, severity grading based on the phenotypic criteria [12].

The GLIM included reduced muscle mass as a phenotypic criterion, an assessment which requires certain techniques and expertise, and may not been so commonly in any clinical or research settings [12,14]. Aware of the challenge that the muscle mass assessment involves, the ESPEN launched the "Guidance for assessment of the muscle mass phenotypic criterion for the GLIM diagnosis of malnutrition", endorsing both specialized, like Dual-Energy X-Ray Absorptiometry (DXA), and anthropometric techniques [14]. Moreover, the new Global Leadership of Sarcopenia (GLIS), a global framework to develop international consensus on definition and diagnosis of sarcopenia has just been formed [15] and recommends muscle quantity assessment by DXA, with measurement of appendicular lean mass (ALM) alone, i.e., not standardized by body size as a ratio, and adjust multivariate models for the body size standardization variable instead [15].

To date, only malnutrition risk screening tools, such as the Mini- Nutritional Assessment Short-For (MNA-SF) [16] have been used to define malnutrition in the IC nutritional (or vitality) domain [3,4,7]; its performance has been shown to be limited [3,4], and no association between IC nutritional domain using the MNA-SF and mortality in community-dwelling population has been found [3]. So far, the ability of IC, using the GLIM criteria to define malnutrition, to predict death have not been assessed yet. Moreover, since

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multiple criteria exists to define a reduced muscle mass as phenotypic criterion in the nutritional domain, it would be interesting to assess the impact of these different criteria on the mortality-risk.

The hypothesis of this research is that an IC construct which incorporates the reference operational definition of malnutrition in adults, as nutritional domain, is associated with a higher 9-year mortality-risk in community-dwelling older people. The hypothesis was tested in the *Sarco*penia and *Ph*ysical Impairment with advancing *Age* (SarcoPhAge) cohort, a study aimed to assess musculoskeletal health and quality of life in older people, where baseline data about IC and GLIM criteria, and mortality at 9-year follow-up are available.

2. Methods

2.1. Objectives

The primary objective of this paper is to assess the ability of IC to predict death using different criteria to define an unsatisfactory nutritional domain: 1) MNA-SF, 2) seven versions of GLIM criteria, varying by the technique used to identify a reduced muscle mass, 3) sequential screening (MNA-SF) *and* diagnosis (GLIM criteria). Secondarily, we aimed to assess the diagnosis concordance between these 3 criteria and the diagnostic performance of 1) the MNA-SF and 2) the seven versions of the GLIM criteria, compared to 3) the combination of the MNA-SF + GLIM criteria.

2.2. Design and settings

This is a post-hoc analysis of the SarcoPhAge cohort, which assessed functional and health outcomes of sarcopenia in community-dwelling older adults in Belgium, during a 9-year follow-up. The baseline included 534 community-dwelling older volunteers, followed-up from 2013 to January 2023. The full methodology of this population-based cohort have been previously published [8,17]. The Guidance on validation of the operational criteria for the diagnosis malnutrition in adults [18] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [19] were followed for this research.

2.3. Intrinsic capacity

Four IC domains were assessed at baseline: nutritional, locomotor, cognition, and psychosocial [2,20]. The assessment of each domain, in each individual, was conducted following the procedures and thresholds of the original validated version of each tool, except for the cognitive domain, where, for study purposes, the threshold was chosen based on updated literature instead [21]. The sensorial was not assessed due to lack of data. For study purposes, the term nutritional domain was preferred in the study over other possibilities [22,23].

For the nutritional domain, the presence of malnutrition indicated an unsatisfactory nutritional domain (dichotomous variable, yes/no) and was defined by: 1) screening by MNA-SF; 2) seven versions of the GLIM criteria, based on the technique used to identify a reduced muscle mass; 3) Both screening and diagnosis by the GLIM criteria. Table 1 provides details about the options to define an unsatisfactory IC nutritional domain [14,15,24]. Regarding the three other IC domains, a Short Physical Performance Battery (SPPB) ≤8

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points (maximum 12 points), indicating disability, was considered as unsatisfactory locomotor domain [20,25,26]; a Mini-Mental State Examination (MMSE) score ≤ 26 points (maximum 30 points) was considered as unsatisfactory cognitive domain [21]**;** and a Geriatric Depression Scale (GDS) score ≥ 5 points (maximum 15 points) was considered as unsatisfactory psychological domain [27].

2.4. Statistical methods

Statistics analysis were conducted by Statistical Package for Social Sciences (SPSS version 24.0; SPSS, Inc., Chicago, IL, USA). For all of the below-described statistics, *p*-values <0.05 % were considered statistically significant. Baseline characteristics of study participants were described for the whole sample and according to the different way of measuring malnutrition in the IC nutritional domain. Normality of continuous variables was checked by the Shapiro-Wilk test, the comparison of mean and median, the histograms and QQ plots. Age, BMI, ALM, ALMI, muscle strength, and gait speed presented a normal distribution and were expressed by mean and standard deviation (SD). All the other variables were skewed and expressed by median (P25-P75).

For the primary objective, the association between an unsatisfactory IC nutritional domain and the 9-year risk of death by Odds ratio (OR) and 95 % confidence interval (CI) was measured. Vital (death/alive) status was recorded by annual follow-up and medical records with linkage to the Belgian death registry. Crude and adjusted OR were obtained using logistic regressions. Two models were calculated: Model 1 used age and sex as covariates; Model 2 used age, sex, number of concomitant diseases, number of drugs, and physical activity level as covariates. ALM was adjusted for the body size standardization variable in the multivariate model, as recommended by GLIS on sarcopenia [15].

For the secondary objective, the diagnostic accuracy of the different techniques was measured. The following diagnostic performance indicators were measured: sensitivity, specificity, Youden index, positive (PPV) and negative (NPV) predictive values, and Area Under the Curve (AUC) for each diagnosis techniques compared to sequential screening (MNA-SF) *and* diagnosis (GLIM criteria with ALMI) (reference standard) [11,14,18]. An assessment method was considered to have poor performance indicators if sensitivity or specificity <50 %; fair, if sensitivity or specificity <80 %, but both values >50 %; and good, if sensitivity and specificity >80 % [28]. The Youden index summarized sensibility and specificity, ranging from 0 to 1, 0 indicates that the assessment method is useless and 1, indicates perfect sensitivity and specificity. The Cohen-kappa coefficient (k) was calculated to assessed the concordance (or agreement) between all techniques: A k < 0 indicates disagreement; 0–0.20, very slight agreement; 0.21–0.40, low agreement; 0.41–0.60, moderate agreement; 0.61–0.80, strong agreement; and 0.81–1, almost perfect agreement [8]. For the present analysis, all participants of the SarcoPhAge study were included (*n* = 534), as the outcome (i.e., death) was available at 9- year follow-up for the whole cohort. However, among the 534 participants, IL6 and IGF1 measures, which were used as an etiologic criterion of the GLIM definition, were only collected on a sample of the population (*n* = 411, 77 % of the total sample). A sensitivity analysis, including only the 411 participants with full data available was further performed.

2.5. Ethics

The study was conducted according to the Good Clinical Practice Guidelines, the Declaration of Helsinki, and its later amendments. Data were treated in accordance the General Data Protection Regulation

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2016/679 of the European Parliament and Council. The study was approved by the Liege University Ethics Committee (ref.2012/277). Informed consent was signed by all participants.

Table 1
Summary table of the different techniques used to define an unsatisfactory IC nutritional domain at baseline in the study.

Screening for malnutrition by the MNA-SF ≤11 (maximum 14 points)						
		Phenotypic criteria			**Etiologic criteria**	
		Weight loss	**Low BMI**	**Reduced muscle mass criterion**	**Reduced food intake or assimilation**	**Inflammation**
Unsatisfactory IC nutritional domain	**Diagnosis of malnutrition according to the GLIM criteria in the SarcoPhAge study (at least one phenotypic AND at least one etiologic criteria)**	Weight loss ≥4.5 kg in the past 12 months by clinical interview	Reduced if <22 kg/m^2 in ≥70-year-old and <20 kg/m^2 in <70-year-old	7 criteria were used: 1. ALM alone: men <20 kg, women<15 kg[a] 2. ALM adjusted for height^2 (ALMI): men <7 kg/m^2, women<5.5 kg/m^2[b,c] 3. ALM adjusted for weight: men <25.7 %, women<19.4 %[c] 4. ALM adjusted for BMI: men <0.827 women<0.518[c] 5. Calf-circumference: <31 cm[b,c] 6. Sex-adjusted, BMI-adjusted calf circumference: men <33 cm, women<32 cm[c,d] 7. Mid-arm circumference: <26 cm[e]	The question "Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?", as first item of the MNA-SF was administered. A positive answer was considered in presence of moderate and severe decrease of food intake	Sex dependent quartiles for IL-6 and IGF-computed for SarcoPhAge. The lowest sex-specific quartile was stablished as threshold: IL-6 >3.84 pg/mL in men and >2.99 pg/mL in women and IGF-1 ≤88 ng/mL in men and ≤82 ng/mL in women. Disease burden was not measured.
Unsatisfactory IC locomotor domain (SPPB ≤8 points, /12)						
Unsatisfactory IC cognitive domain (MMSE ≤26 points, /30)						
Unsatisfactory IC psychological domain (GDS ≥5 points, /15)						

ALM: Appendicular lean mass; **BMI:** body mass index; **DXA:** dual energy x-ray absorptiometry; **GLIS:** Global Leadership Initiative on Sarcopenia; **MMSE:** Mini-Mental State Examination; **MNA-SF:** Mini-Nutritional Assessment Short Form; **SPPB:** Short Physical Performance Battery.

[a] Recommendation from the GLIS on sarcopenia.
[b] Recommendation from the revised consensus on definition and diagnosis on sarcopenia (European Working Group on Sarcopenia in Older People 2, EWGSOP2).
[c] Recommendation from the ESPEN Guidance for assessment of the muscle mass phenotypic criterion for the GLIM.
[d] In adults with obesity, decrease the measured value by 3 cm (BMI, 25–30) or 7 cm (BMI, 30–40).
[e] The threshold <26 cm for mid-arm circumference was the specific lower quartile calculated for the SarcoPhAge cohort.

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Table 2
Nine-year follow-up death and its association with unsatisfactory IC domains at baseline in the SarcoPhAge cohort (N =534).

			MNA-SF ≤11 points as unsatisfactory IC nutritional domain		
	Yes (n = 115)	**No (n = 419)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	51 (44.3)	106 (25.3)	2.35 (1.53–3.61)	2.80 (1.72–4.56)	2.38 (1.44–3.95)
			Malnutrition according to the GLIM criteria with ALMI (ALM/height²) in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
	Yes (n = 101)	**No (n = 433)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	47 (46.5)	110 (25.4)	2.57 (1.63–3.99)	2.94 (1.79–4.85)	2.59 (1.53–4.37)
			Malnutrition according to the GLIM criteria with ALM/weight in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
Nine-year follow-up death (n, %)	46 (52.3)	111 (24.9)	3.3 (2.07–5.29)	3.15 (1.88–5.28)	2.66 (1.56–4.56)
			Malnutrition according to the GLIM criteria with ALM/BMI in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
Nine-year follow-up death (n, %)	56 (44.8)	101 (24.7)	2.47 (1.63–3.76)	2.18 (1.38–3.44)	1.77 (1.10–2.85)
			GLIM criteria with reduced ALM alone, as the muscle quantity approach recommended by the GLIS on sarcopenia in the phenotypic criterion, as unsatisfactory IC nutritional domain		
Nine-year follow-up death (n, %)	52 (44.4)	105 (25.2)	3.09 (1.91–4.74)	2.83 (1.73–4.63)	2.47 (1.48–4.13)
			Malnutrition according to the GLIM criteria with ESPEN-endorsed calf-circumference in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
Nine-year follow-up death (n, %)	39 (48.8)	118 (26.0)	2.71 (1.67–4.40)	2.84 (1.66–4.86)	2.45 (1.39–4.31)
			Malnutrition according to the GLIM criteria with calf-circumference computed for SarcoPhAge in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
	Yes (n = 81)	**No (n = 453)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	40 (49.4)	117 (25.8)	2.80 (1.73–4.54)	2.92 (1.71–5.00)	2.49 (1.41–4.39)
			Malnutrition according to the GLIM criteria with mid-upper arm circumference in the reduced muscle mass phenotypic criterion, as unsatisfactory IC nutritional domain		
Nine-year follow-up death (n, %)	34 (50.0)	123 (26.4)	2.79 (1.66–4.68)	2.99 (1.69–5.31)	2.74 (1.50–4.98)
			Sequential screening by the MNA-SF ≤11 *and* diagnosis according to the GLIM criteria with ALMI (ALM/height²), as unsatisfactory IC nutritional domain		
	Yes (n = 58)	**No (n = 476)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	31 (53.4)	126 (26.5)	3.19 (1.83–5.55)	3.73 (1.99–6.97)	3.27 (1.72–6.23)
			Unsatisfactory IC locomotor domain (SPPB ≤8 points, /12)		
	Yes (n = 151)	**No (n = 483)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	71 (47.0)	86 (22.5)	3.06 (2.05–4.57)	3.04 (1.87–4.93)	2.31 (1.38–3.86)
			Unsatisfactory IC cognitive domain (MMSE ≤26 points, /30)		
	Yes (n = 94)	**No (n = 440)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	42 (44.7)	115 (26.1)	2.28 (1.44–3.61)	1.69 (1.01–2.82)	1.47 (0.86–2.51)
			Unsatisfactory IC psychological domain (GDS ≥5 points, /15)		
	Yes (n = 175)	**No (n = 359)**	**Crude OR (95 %CI)**	**Model 1 OR (95 %CI)**	**Model 2 OR (95 % CI)**
Nine-year follow-up death (n, %)	69 (39.4)	88 (24.5)	2.00 (1.36–2.95)	2.39 (1.55–3.67)	1.78 (1.12–2.83)

ALM: Appendicular lean mass; **ALMI:** Appendicular lean mass index; **BMI:** Body mass index; **ESPEN:** European Society of Clinical Nutrition and metabolism; **GDS:** Geriatric Depression Scale; **GLIM:** Global Leadership Initiative on Malnutrition; **GLIS:** Global Leadership Initiative on Sarcopenia; **IC:** Intrinsic capacity; **MMSE:** Mini-Mental State Examination; **MNA-SF**: Mini-Nutritional Assessment Short Form; **SPPB:** Short Physical Performance Battery.
Model 1: Age and sex as covariates. / Model 2: Age, sex, number of concomitant diseases, number of drugs, and physical activity level as covariates.

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Table 3
Performance indicators of the possibilities for the IC nutritional domain: 1) the MNA-SF, 2) the GLIM criteria using the muscle mass quantity approach recommended by the GLIS on sarcopenia and the Guidance for assessment of the muscle mass phenotypic criterion, compared to the presence of malnutrition according to the sequential screening by the MNA-SF *and* the diagnosis by GLIM criteria with ALMI (ALM/height^2), assessed by DXA in the reduced muscle mass phenotypic criterion (reference standard).

	Se (%) 95 % CI	Sp (%) 95 % CI	Youden index	PPV (%) 95 % CI	NPV (%) 95 % CI	AUC 95 % CI
MNA-SF ≤ 11 points	100.0 % (93.8–100)	88.0 % (84.8–90.8)	0.88	50.4 % (44.4–56.5)	100.0 %	0.75 (0.69–0.81)
GLIM criteria with ALMI (ALM/height^2) in the reduced muscle mass phenotypic criterion	100.0 % (93.8;100)	90.9 % (88.0–93.4)	0.91	57.4 % (50.3–64.2)	100 %	0.79 §0.72–0.85)
GLIM criteria with ALM/weight in the reduced muscle mass phenotypic criterion	82.8 % (70.6–91.4)	91.6 % (88.7–93.9)	0.74	54.5 % (46.6–62.3)	97.8 % (96.1–98.7)	0.76 (0.69–0.83)
GLIM criteria with ALM/BMI in the reduced muscle mass phenotypic criterion	84.5 % (72.6,92.6)	84.0 % (80.4–87.2)	0.69	39.2 % (33.8–44.9)	97.8 % (96.0–98.8)	0.68 (0.62–0.75)
GLIM criteria with reduced ALM alone, as the muscle quantity approach recommended by the GLIS on sarcopenia in the phenotypic criterion	94.8 % (85.6–98.9)	86.9 % (83.6–89.9)	0.82	47.0 % (41.1–53.0)	99.3 % (97.9–99.8)	0.73 (0.67–0.79)
GLIM criteria with ESPEN-endorsed calf-circumference in the reduced muscle mass phenotypic criterion	87.9 % (76.7–95.0)	93.9 % (91.4–95.9)	0.82	63.7 % (54.9–71.7)	98.5 % (96.9–99.2)	0.81 (0.74–0.88)
GLIM criteria with calf-circumference computed for SarcoPhAge in the reduced muscle mass phenotypic criterion	86.2 % (74.6–93.8)	93.5 % (90.9–95.5)	0.8	61.7 % (53.1–69.7)	98.2 % (96.7–99.1)	0.80 (0.73–0.87)
GLIM criteria with mid-upper arm circumference in the reduced muscle mass phenotypic criterion	82.8 % (70.6–91.4)	95.8 % (93.6–97.4)	0.79	70.6 % (60.6–78.9)	97.8 % (96.3–98.8)	0.84 (0.78–0.91)

ALM: Appendicular lean mass; **ALMI:** Appendicular lean mass index; **AUC**: Area under the ROC curve; **BMI:** Body mass index; **ESPEN:** European Society of Clinical Nutrition and metabolism; **GLIM:** Global Leadership Initiative on Malnutrition; **GLIS:** Global Leadership Initiative on Sarcopenia; **IC:** Intrinsic capacity; **MNA-SF**: Mini-Nutritional Assessment Short Form; **SPPB:** Short Physical Performance Battery; **Se**: sensitivity; **Sp**: specificity; **PPV**: positive predictive value; **NPV**: negative predictive value.

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3. Results

The SarcoPhAge cohort included 534 participants. **Appendix 1** summarizes the baseline characteristics of the study participants according to the IC nutritional domain. The median age was 73.5 ± 6.16- year-old, 322 (60.3 %) were women, with BMI 26.6 ± 4.77 kg/m2. The prevalence of an unsatisfactory IC nutritional domain, i.e., malnutrition, ranged from 10.9 % using the combination of both MNA-SF and GLIM to 23.5 % using the GLIM with ALM alone.

Out of 534 participants included at baseline, 157 (29.4 %) were dead at the 9-year follow-up. Table 2 shows the associations between 9-year death and the baseline unsatisfactory IC domains. Having any of the IC domains unsatisfactory at baseline was predictive of 9-year death, and these associations remained significant after adjustment (both in Model 1 and 2). The highest prediction for 9-year mortality was shown in participants with a baseline unsatisfactory IC nutritional domain by a sequential screening by the MNA-SF *and* diagnosis according to GLIM criteria with ALMI [fully adjusted-OR = 3.27 (95%CI 1.72–6.23)]. Sensitivity analyses, including only participants in which inflammation was measured (*n* = 411), confirmed the results. Stronger associations were even found (**Appendix 2**). Two other IC domains were also predictive of death: adjusted-OR = 2.31 [95%CI 1.38–3.86] for unsatisfactory locomotor domain and adjusted-OR = 1.78 [1.12–2.83] for unsatisfactory psychological domain. Unsatisfactory cognitive domain was however not significantly predictive of death (adjusted-OR = 1.47 [95%CI 0.86–2.51]).

Performance indicators for the different techniques to measure an unsatisfactory IC nutritional domain compared to the sequential screening by MNA-SF and GLIM criteria are available in Table 3. Sensibility and specificity values were high (all above 82 %). The highest sensitivity found was of 100 % using the MNA-SF alone or the GLIM with ALMI. The highest specificity found was of 95.8 % using the GLIM with mid-upper arm circumference. The highest Youden index was found for the GLIM with ALMI (i.e., 0.91). The concordance between all techniques using Kappa coefficient is reported in **Appendix 3**. Overall, the agreement was strong to almost-perfect for all techniques, meaning that they identified almost the same individuals, except for the MNA-SF, which showed very-slightly-to-low agreement with the other criteria.

4. Discussion

Our study showed that baseline unsatisfactory IC domains predicted two-fold to 3.5-fold higher 9-year mortality-risk in community-dwelling older people and that the highest predictive capacity was achieved when the IC nutritional domain incorporated sequential screening by the MNA *and* diagnosis by GLIM criteria. With the exception of the MNA-SF, which showed very-slightly-to-low agreement with the rest of the techniques and surrogate markers, all techniques showed good and strong diagnostic performance indicators and concordance, respectively, supporting Guidance's statement "no criterion-standard or superior technique is currently acknowledged, and use of different techniques should be based on availability criteria" [14].

The recommendation of the new GLIS on sarcopenia, ALM alone assessed by DXA, was associated to 2.5-fold higher 9-year mortality-risk and showed strong-to-almost perfect agreement with all techniques and surrogate markers. To our knowledge, this is the first study which explores the GLIS on sarcopenia

recommendation, i.e., ALM alone, in light of other techniques [14,15]. The rationale for the recommendation of the ALM alone is to avoid the potential spurious associations linked to the use of ratios and due to concerns that adjustment for the standardization factor (i.e., height, weight, or BMI) in a multivariate model may challenge the interpretation of the effect estimates [14,15]. Further studies are needed to explore its predictive validity for priority person- centered outcomes, other than mortality, such as quality of life. Being engaged in a healthy lifestyle and regular physical activity have been shown to be key elements for maintenance of muscle mass and function and having a higher quality of life, in general population and in midlife and beyond [29]. Socio-environmental and contextual factors, such as higher income and education, have been shown to be related to a greater practice of physical activity and a higher quality of life in older people [30]. Therefore, it is crucial to promote and educate about healthy lifestyle and physical activity at all ages, towards a healthy ageing [29,30].

The sequential screening by the MNA-SF *and* diagnose by GLIM criteria, as unsatisfactory IC nutritional domain, achieved the strongest predictive capacity for 9-year mortality-risk. This result may be explained by the fact that the combination is stricter, obtained a lower prevalence of malnutrition, and therefore probably identified participants with the worst nutritional status. The findings are aligned with the Vienna Declaration's recommendation that "Nutritional care should be provided in a systematic sequence" [11]. An additional advantage may be that the two-step IC nutritional domain would be probably much more efficient (cost, time, etc.), but this hypothesis was not assessed in the study and requires further research.

Evidence about the GLIM criteria in the IC nutritional domain was unavailable and necessary for their joint use, because the IC construct and the WHO ICOPE guidelines are targeted at community-dwelling older people and their health care providers, including those healthcare settings with limited access to specialized geriatric and nutritional care [7,14]. Since the development of the IC and the WHO ICOPE Guidelines [7], and in the framework of the Decade of Healthy Ageing 2021–2030, the WHO has gathered initiatives to shed light on the IC construct, and the assessment methods for each domain, in order to select those with the highest prognosis capability and feasible for person-centered assessment [7], e.g., the ongoing WHO Locomotor capacity working group, among others [20,31]. Moreover, the WHO Europe has recently engaged the ESPEN as a non-State Actor in September 2022, as the principles of the two institutions towards the advancement of Public Health are aligned. Our study shed light on the reference operational definition of malnutrition in adults within the IC construct, confirmed that it retrieved the highest prognosis information, and that may be helpful to develop and guide specific WHO Public Health actions in older people in the Decade of Healthy Ageing [7,20].

Some limitations may be acknowledged. First, the post-hoc nature of the study, may be seen as a limitation. This is a minor issue, in presence of the highest methodological quality, which meets the highest quality standards for cohort and diagnostic accuracy studies and the GLIM Guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults [18]. Moreover, the study counts on a large sample with complete data at 9-year follow-up, which is, to authors' knowledge, the longest follow-up about GLIM criteria [32] and equals the longest follow-up reported about IC [5]. Second, the sensory domain was not collected, as insufficient information was available for the baseline assessment of the SarcoPhAge study. The missing domain does not affect the association with mortality of the rest of the domains, but may hinder the study providing a global understanding of the IC construct. Despite the influence of declines in this domain on mortality has been shown [33], it is rarely addressed, and could be highlighted as a topic for further research. Third, we decide to include all participants in the main analysis, including those with no inflammatory measurement, which is one of the etiology criteria of the diagnosis of malnutrition. This may be considered as a limitation as a complete assessment of malnutrition was not

performed on these participants. The rationale for the decision of including the whole study sample at baseline was 1) To include in the analysis the largest possible sample, 2) Because data about the main outcome and three of the four IC domains were available in the whole sample, 3) Because the baseline characteristics of the participants in the SarcoPhAge cohort, which included healthy community-dwelling older volunteers, had previously shown low prevalence of inflammatory conditions (102/411 participants, 24 %) [17]. To check for the potential impact of this decision on the external validity of the results, we performed a sensitivity analysis excluding the participants without any measure of IL6 or IGF1 at baseline. Results remained consistent in the sensitivity analysis. Stronger associations, with higher OR were even found when restricted the sample to participants with all available data, suggesting that the association between malnutrition and death reported in this paper may have been underestimated. Third, the two-step screening and diagnosis process was explored only for GLIM with ALMI, a minor issue, due to the strong concordance among techniques. Fourth, as a matter of consistency with previous publications on the SarcoPhAge study using the GLIM criteria to define malnutrition status [8,17,34], we used the sex-dependent quartiles of IL6 or IGF1 to define the inflammation etiologic criteria. Those markers were chosen in accordance with the recommendations by the Targeting Ageing with MEtformin Biomarkers Workgroup for the selection of blood-based biomarkers for geroscience-guided clinical trials [35]. However, IGF1 is a nutrient signaling marker and the choice of using it in the etiologic criteria for inflammation in GLIM may be discussed. As a matter of transparency, we performed an extra sensitivity analysis using only IL6 as etiologic criteria for inflammation. In this sensitivity analysis, the prevalence of malnutrition was obviously lower than the prevalence found when combining both IL6 or IGF1 criteria, but similar and still significant effect sizes were found to emphasize the relationship between baseline malnutrition and the 9-year follow-up mortality risk (*data not shown and available under request*). Finally, a selection bias involving the study population may has occurred, as the scope of the study about musculoskeletal health and quality of life may have aroused the interest of those individuals with awareness about the topic and a better health status.

Our findings involve theorical implications for scientific scholars, as support the two-step nutritional care process and the use of the GLIM criteria within the IC construct, as they highly increased the predictive value for 9-year mortality. Moreover, the findings also involve clinical implications for the population in midlife and beyond and their healthcare providers, as malnutrition is a reversible condition, and is crucial to recognize the true magnitude of the association between malnutrition and death for an effective prevention, early identification and management, and resource allocation to reduce nutrition-related mortality rates and improve key health outcomes. Our findings are consistent with previous literature, as an early detection of decreased IC has been associated to an increased risk of death, incident dependence, and incident disability, independently of health status [3,36], which highlights the potential of IC and its domains as key endpoints of individual and Public Health Actions towards healthy ageing. The term "nutritional domain" was considered more appropriate for the study purposes because it more precisely described its aims and scope, specifically focusing on the assessment of malnutrition. This term is still a subject of debate, as some authors have referred to this domain as "nutritional domain" [3], others as "vitality" [22], others as "vitality/ nutrition" [23], and some authors include nutrition as one component of the broader vitality domain [37]. Future lines of research may continue harmonizing the major advances in the field of nutrition and nutrition- related diseases achieved in the past decades within the framework of the WHO IC construct. For instance, IC research may benefit from incorporating new methodological approaches which have shown to be efficient in malnutrition, sarcopenia, and frailty, and have not been explored yet in the framework of the WHO IC approach, e.g., development of pragmatic trials (designed to

evaluate the effectiveness of care options or interventions in unselected patients in real-life clinical practice conditions) or identification of the Core Outcome Set for IC intervention studies.

5. Conclusions

The study showed that baseline unsatisfactory IC domains predicted two-fold to 3.5-fold higher 9-year mortality-risk in community-dwelling older people. The highest predictive capacity was achieved when the IC nutritional domain incorporated sequential screening by the MNA-SF and diagnosis by GLIM criteria, with a 3.5-fold higher 9-year mortality risk. With the exception of the MNA-SF, which showed very-slightly-to-low agreement with the rest of the techniques and surrogate markers, all techniques showed good and strong diagnostic performance indicators and concordance among them. Incorporating the reference operational definition of malnutrition as unsatisfactory IC nutritional domain could be helpful to guide Public Health Actions towards Healthy Ageing.

Contributors

D Sanchez-Rodriguez wrote the manuscript and did the literature review.

C Demonceau revised the manuscript.

O Bruyère participated in data collection and revised the manuscript.

E Cavalier revised the manuscript.

J.-Y. Reginster revised the manuscript.

C Beaudart wrote the manuscript, did the literature review, participated in data collection, analysed and interpreted data, and revised the manuscript.

All authors read and approved the final version of the manuscript.

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Ethical approval

The study was conducted according to the Good Clinical Practice Guidelines, the Declaration of Helsinki, and its later amendments. Data were treated in accordance the General Data Protection Regulation 2016/679 of the European Parliament and Council. The study was approved by the Liege University Ethics Committee (ref.2012/277). Informed consent was signed by all participants.

Provenance and peer review

This article was not commissioned. Peer review was directed by Cedric Annweiler, independently of Dolores Sanchez-Rodriguez, an author and member of the *Maturitas* editorial board, who was blinded to the process.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

DS-R, OB, Y-IR, and CB serve as Senior Advisors to the World Health Organization (WHO) Collaborating Center for Epidemiology of Musculoskeletal Health and Ageing, Division of Public Health, Epidemiology, and Health Economics, University of Liège, Liège, Belgium. Y-IR serves as a member of the Board of Directors of the Clinical Consortium on Healthy Ageing (CCHA) of the WHO, Geneve, Switzerland. DS-R and OB serve as Editorial Board members of Maturitas. All authors declare they do not have any personal or financial relationships with other organizations or people that could inappropriately influence their work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.107817.

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