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Original article

Global Leadership Initiative on Malnutrition (GLIM): Guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults☆

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SUMMARY

Background: The Global Leadership Initiative on Malnutrition (GLIM) created a consensus-based framework consisting of phenotypic and etiologic criteria to record the occurrence of malnutrition in adults. This is a minimum set of practicable indicators for use in characterizing a patient/client as malnourished, considering the global variations in screening and nutrition assessment, and to be used across different health care settings. As with other consensus-based frameworks for diagnosing disease states, these operational criteria require validation and reliability testing as they are currently based solely on expert opinion.
Methods: Several forms of validation and reliability are reviewed in the context of GLIM, providing guidance on how to conduct retrospective and prospective studies for criterion and construct validity.
Findings: There are some aspects of GLIM criteria which require refinement; research using large data bases can be employed to reach this goal. Machine learning is also introduced as a potential method to support identification of the best cut-points and combinations of operational criteria for use with the different forms of malnutrition, which the GLIM criteria were created to denote. It is noted as well that the validation and reliability testing need to occur in a variety of sectors, populations and with diverse persons completing the criteria.

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Conclusion: The guidance presented supports the conduct and publication of quality validation and reliability studies for GLIM.

1. Background

Clinical nutrition researchers have for more than a decade been interested in developing common terminology and criteria for the identification of malnutrition across global health care sectors. Over time, the malnutrition definition has changed due to greater knowledge and awareness of the role of inflammation and the impact body composition derangements play on outcomes related with this condition. Malnutrition is defined here as a subacute or chronic state of nutrition, in which a combination of varying degrees of under- or overnutrition and inflammatory activity has led to changes in body composition and diminished function [1–4]. Malnutrition may be corrected or improved by interventions that enhance food/nutrient intake and meet requirements [5] but in the presence of inflammation, such as in disease-related malnutrition, the benefits of nutrition treatment may be blunted [6]. International guideline committees have agreed on the etiologic basis of the undernutrition form of malnutrition as resulting from decreased intake and/or assimilation of energy and protein intake and/or inflammation resulting in catabolism of lean tissues, with further categorization of malnutrition associated with: a) chronic disease or conditions with sustained inflammation, b) chronic disease with minimal or no perceived inflammation, c) acute disease or injury with severe inflammation, or d) pure chronic starvation not related to disease [3,7]. The Global Leadership Initiative on Malnutrition (GLIM) used a consensus-based approach to produce operational criteria for these various forms of malnutrition using a minimum of one phenotypic and one eticologic component. These are known as the 'GLIM criteria'.

The GLIM operational diagnostic criteria are based on the *minimum* phenotypic and etiologic criteria of: significant weight loss OR low body mass index OR low muscle mass AND reduced food intake or its assimilation OR inflammation [8,9]. These are *operational criteria,* in that they operationalize the consensus based definitions of malnutrition and the more specific subcategories based on the etiology of impaired nutritional intake, reduced assimilation, and exacerbation of these by inflammation due to chronic or acute disease. Significant weight loss, low BMI and/or low skeletal muscle mass are clinical features expressing (the severity of) malnutrition.

It is important to provide some points of clarification on the GLIM criteria. First, these are criteria that are designed to be used globally, in different healthcare sectors, to provide a common basis for diagnosis; this is not a 'new' definition of malnutrition. However, it is unclear if these criteria are valid in all of these scenarios. Further, they are a 'minimum criteria' for the diagnosis of malnutrition globally, recognizing the varying capacities and traditions of regions and health care systems for the conduct of nutrition assessment to diagnose malnutrition. As well, these operational criteria do not identify micronutrient malnutrition, but only protein-energy malnutrition and specifically, undernutrition. Finally, they are based on consensus of experts, who although world leaders, have the potential for bias that influenced the development of these criteria. As with any new tool, validation of these criteria are important to support their dissemination and uptake into practice.

This paper will provide a brief overview of how GLIM criteria were developed, guidance on how they should be positioned for use in nutrition care, and how they are to be validated and tested for reliability with retrospective or prospective studies.

2. Overview of GLIM criteria & development

The GLIM operational diagnostic criteria were developed over a period of three years (2016–2018) by collective leadership of four major clinical nutrition societies (American Society for Parenteral and Enteral Nutrition [ASPEN], European Society for Clinical Nutrition and Metabolism [ESPEN], Federación Latinoamericana de Terapia Nutricional, Nutrición Clínica y Metabolismo [FELANPE], Parenteral and Enteral Nutrition Society of Asia [PENSA]). Representatives from diverse disciplines, considered leaders in their societies, were invited to participate and act for their societies. At face-to-face meetings, these leaders shared their region's current practices and challenges in the diagnosis of malnutrition; developed a common understanding of the phenotype and etiology of malnutrition using extant research; compared and contrasted screening and assessment tools for common nutrition indicators; and identified and ranked by secret ballot the minimum indicators that should be included [8,9]. As such, GLIM criteria are consensus-based and validation is needed to confirm, and if necessary, refine these operational criteria. Within the medical field this is an accepted process; evidence-informed consensus has been used to develop diagnostic criteria which are then validated and refined at regular timepoints (e.g., Alzheimer's disease dementia [10], multiple sclerosis [11], and sarcopenia [12]).

Cut-points for defining a significant weight loss, low BMI and reduced food intake were based on prior evidence where available (e.g. weight loss, BMI) or based on the best judgment of the GLIM group. Details on how to categorize inflammation, low muscle mass and reduced assimilation of food intake due to gastrointestinal conditions are not yet provided due to a lack of clearly defined cut-points or markers. Phenotypic indicators are used to determine severity of malnutrition. Validation studies during the next few years will be crucial in determining whether the suggested framework works in practice and will help to develop cut-points and further definition of the operational criteria for disease state/inflammation, muscle mass assessment and assimilation of food, and in evaluating whether malnutrition severity criteria are appropriate.

2.1. Positioning GLIM criteria within nutrition care

As outlined in the GLIM consensus report, screening and assessment processes occur outside of, and feed into, the GLIM operational diagnostic criteria [8,9]. GLIM does not replace current validated screening and assessment tools but rather is used *along side of* these tools to offer minimum criteria for the classification or description of a patient as malnourished. As noted above, GLIM is not comparable to, nor does it replace a comprehensive nutrition assessment in clinical care. These minimum operational criteria are needed globally to speak one language across the world, to understand the variation in prevalence of protein-energy malnutrition among regions and populations, as well as to support the development of an updated International Classification of Diseases coding for malnutrition [8,9].

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The consensus-based definition of risk screening is 'a rapid process performed to identify subjects at nutritional risk' [3]. There is a wide variety of valid and reliable screening tools often created for specific populations or health care settings. These tools may identify patients already malnourished, at risk of malnutrition, or assess risk factors that may result in malnutrition in the future. As a rapid tool, they typically require minimal expertise and only include a few nutrition indicators or risk factors. Assessment on the other hand provides a 'basis for the diagnosis decision, as well as for further actions including nutritional treatment' [3]. A clinical nutrition assessment completed by a trained health care professional (e.g., dietitian, physician) has many components including adequacy of food intake in comparison to nutritional requirements, functional ability (and growth for children), clinical/medical history, physical exam, weight history, body composition, and biochemical assessment [4,13], with specific components, standards and references often particular to a population group (e.g., head circumference in children). A comprehensive assessment can lead to a diagnosis of undernutrition, overnutrition, or micronutrient deficiency or excess. Due to its in-depth nature, a comprehensive nutrition assessment provides details that are needed to understand the root causes of the malnutrition, guide interventions and monitoring, and anticipate outcomes based on severity of malnutrition. To standardize clinical practice and advance research in malnutrition, a few valid and reliable assessment tools have been created which are more comprehensive than screening tools, but less thorough than a complete clinical nutrition assessment (e.g., Subjective Global Assessment [14], Mini-Nutritional Assessment (for older adults) [15] and Patient-Generated Subjective Global assessment (for patients with cancer [16,17]). These tools specifically target protein-energy malnutrition, as this has been the greatest concern with respect to healthcare use in much of the developed world.

When developing GLIM, emphasis was placed on criteria that would reflect the protein-energy malnutrition definition [1,3], while being appropriate for diverse settings and contexts (e.g., outpatient clinics; ICU; acute care; residential care; community etc.) and throughout the world (both in high income and low income countries, applicable to different ethnicities). To fulfill the ideal that the criteria should be applicable everywhere, without the need for (expensive) diagnostic equipment, practicability of included parameters was a prerequisite [18,19]. Due to the dichotomous nature of GLIM criteria and time frames (e.g., 6 months weight change), they are not anticipated to be useful to monitor changes in nutritional status post treatment, nor was this the intent of GLIM.

2.2. Guidance on validation of GLIM criteria

As noted in the consensus reports [8,9], the next step in this initiative is to validate and further detail these operational criteria. Validity is the extent to which GLIM criteria identifies what it is intended to identify, i.e. protein-energy malnutrition (Note: the term 'identify' is used here rather than 'measure' as GLIM is not explicitly a measurement tool but a diagnostic framework based on several measures). It should be noted that this is a quite different from a tool that predicts outcomes known to be associated with malnutrition (e.g., length of stay). Table 1 provides an overview of types of validation and a hierarchy which can be used to test validity.

There are several forms of validation, the lowest being face or content validity and the best form of validation being concurrent criterion validity, which is determined by comparing a test tool to a "gold standard" [20–22]. GLIM criteria are considered to have face validity, in that they were developed by an evidence-informed consensus group of experts, including voting on which nutrition indicators should be included [8,9].

Although the experts were appointed by the four nutrition societies involved and were selected to represent different professions, disciplines and regions, their appointments may have had the potential to introduce bias, as they were all selected and agreed to work towards developing universal criteria. This is why face and content validity are insufficient for a diagnostic framework like GLIM. Face validation with typical practitioners was not formally completed, although society representatives may have vetted early versions with their peers. Indicators used are considered relevant to the diagnosis of malnutrition and for the most part, are acceptable and practicable to end-users [21]. Content validity is focused on the inclusion of all relevant concepts and exclusion of irrelevant concepts as judged by experts [19]; this is done by including key questions or items that represent subcomponents of the concept. To confirm validity these selected items need to demonstrate that they represent the domain of interest (e.g., inclusion of inflammatory conditions adequately represents inflammation in the GLIM criteria) [19]. In the case of GLIM, key components crossing diverse areas of nutrition assessment (e.g., weight, inflammation, food intake) are included, but confirmation of their value in representing the subcomponent is needed.

The preferred form of validation is criterion validity, comprising both concurrent and predictive validity. In this situation, there is an understanding of what the concept of malnutrition is and it can be measured in a valid and reliable way. A gold-standard is sometimes the term used to describe a criterion. In the absence of a world-wide gold standard for malnutrition, an in-depth nutritional assessment completed by a trained nutritional expert is regarded as a semi-gold standard [23] and the preferred tool for criterion validation. Nutritional assessment comprises many aspects related to nutritional status, including assessment of dietary intake in relation to requirements, weight history, biochemistry, body composition, factors impeding nutritional intake, physical, psychological and social wellbeing, disease history, and financial status [24, 25]. Subjective Global Assessment or Mini Nutritional Assessment (for older adults), which are brief, standardized tools, have been validated against a nutritional assessment by a clinician [14,15]; they are thus considered 'fuzzy, semi-gold' standards and will be appropriate, but less conclusive at determining validity of GLIM than a comprehensive nutrition assessment [23,26]. Concurrent criterion validity would be the collection of GLIM criteria at the same time as the completion of the (semi-)gold standard criterion. As GLIM is essentially a minimum list of key indicators to identify malnutrition, there may be special challenges in criterion validation. Specifically, there is a high likelihood for criterion contamination if the GLIM criteria are already embedded into the criterion measure being used. Prior work has criticized a variety of screening tools for this issue [18,23].

Often a gold or semi-gold standard is not available and prediction of a meaningful health outcome that is known to be associated with malnutrition can be used; this is called predictive criterion validity [19]. In this form of criterion validity, GLIM criteria would be expected to predict a meaningful outcome that is known to be associated with protein-energy malnutrition (e.g., 6-month mortality). It is important to note however, that predictive validity for meaningful health outcomes does not confirm that GLIM identifies the construct of interest (i.e., protein-energy malnutrition), but that it is identifying something that is associated with the health outcome chosen in the analysis. Health outcomes for use in predictive validity may depend on the setting in which GLIM is used. For example, in the hospital sector, 30- or 60-day readmission are relevant outcomes, whereas in the community sector it may be 12-

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Table 1
Definitions of types of validity and guidance on when and how various forms can be assessed.

Type of validity	Definition	Detailed Description	Methodological Considerations
1. Criterion	Measures or identifies what it is intended to.	When a measure is considered by the field to represent or diagnose the health condition, it is described as the gold standard. Comparison of the test measure to this gold standard demonstrates criterion validity and is the ultimate form of validity as it confirms that the new tool identifies what it is intended to. In the case of GLIM, the gold standard would need to it identify protein-energy malnutrition, as this is what GLIM was designed to identify.	See Concurrent and Predictive Validity
1a. Concurrent	The test measure is compared to a gold standard measure (i.e., criterion) that is collected at the same point in time.	This is one form of criterion validity, which can only be established with an accepted gold standard for malnutrition.	The test measure is compared to the gold standard, which are collected concurrently. It can be completed in relatively few studies, based on different populations.
1b. Predictive	Ability of the test measure to predict a future outcome.	This is another form of criterion validity, but not as confirmatory as a gold-standard criterion comparison. When a gold standard criterion is not available, this form of validity is a substitute, but needs construct validity to further demonstrate the relevance of the tool. In the case of GLIM this would be comparison to meaningful health outcomes that are expected to be associated with protein-energy malnutrition.	Predictive validity is often done in a variety of studies to demonstrate the significance of the test measure when compared to health outcomes. It is important to choose health outcomes relevant to the population and sector, as well as the construct of interest; in this case of GLIM the construct of interest is protein-energy malnutrition.
2. Construct	The test measure is associated with other health constructs or similar tools in the way that is anticipated.	When there is no gold standard, construct validity is necessary to demonstrate the value of the test tool for measuring the construct of interest (i.e., in the case of GLIM, protein-energy malnutrition). If a gold standard exists, construct validity is less of a priority and considered inferior for determining the value of the test tool.	Hypotheses are formulated on how GLIM should be highly correlated with relevant measures/instruments and not with irrelevant measures. A form of construct validity (discriminant) would be if GLIM prevalence is different among groups where prevalence is anticipated to vary (e.g. hospital vs. community). Convergent validity for example, would be finding a positive association between health related quality of life and GLIM criteria. Convergent validity is typically based on other health measures collected at the same time as GLIM criteria.
3. Content and Face	The test measure includes relevant concepts and indicators. This is the lowest form of validity.	This form of validity is established first. Face validity is often completed by experts or knowledgeable practitioners who ensure wording and content are consistent with the concept being assessed. In the case of GLIM, criteria are relevant to protein-energy malnutrition. Content validity is observed when a new tool 'covers' all of the subcomponents of the construct. Face validity confirms that the tool includes measures that are consistent with the construct.	This form of validity is often based on the development process for the new tool. An evidence base and experts are used to identify relevant components and consensus among experts used to derive key components.

or 36-month hospital admission or mortality. Table 2 provides a list of health outcomes for different sectors that may be most relevant.

Construct validity is completed when there is no gold standard or criterion for comparison and a longitudinal study for prediction of outcomes is not possible; this is considered an indirect form of validation [21]. For example, construct validity can involve comparing GLIM criteria to measures of frailty. It would be anticipated that if GLIM criteria were identifying something important that is believed to be protein-energy malnutrition, it should be associated with valid and reliable measures of frailty, as malnutrition and frailty are often co-morbid. This is an example of convergent validity (hypothesized to be associated with the other measure in the expected direction). Divergent validity (hypothesized to not be associated with the other measure) is not as commonly determined; an example would be finding no association between GLIM and body height; it is anticipated that in most health care sectors in the developed world that the height of an adult patient is **not** associated with acute malnutrition. Discriminant validity means GLIM can discriminate among groups where a gradient in the

Table 2
Potential meaningful health outcomes to be used as the comparator in validation studies.

Health care setting	Health outcome
Hospital	In-hospital mortality
	Major complications
	30-days mortality
	30-day readmission rate
	60-day readmission rate
	Length of hospital stay
Nursing home	3-month mortality
	1-year mortality
	Quality of life
	Functionality
Community	Admission rate to hospital or nursing home
	Health care use (e.g., physician visits, hospital)
	Functionality
	Quality of Life

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prevalence of malnutrition is expected. An example of discriminant validity would be having a high prevalence of malnutrition using the GLIM criteria in hospital patients and a lower prevalence in community samples, as it is well known that the prevalence is higher in acute care. These are all forms of construct validity [21]. Validity is not absolute, but a 'matter of degree' [21]. Ongoing assessment of validity and several forms of validity are recommended to confirm the utility of GLIM [22].

2.3. Reliability of GLIM criteria

Reliability is the degree to which the results obtained by a measurement or procedure can be replicated, either by the same assessor or different assessors [27]. Reliability of individual nutrition indicators that make up the GLIM criteria is generally available (e.g., weight, BMI, presence or absence of a disease condition) and adequate, if established protocols for data collection and manipulation (e.g., calculation of percent weight change) are followed. Laboratory measures of inflammation should be considered when rigorous validation testing is the objective to promote reliability; however underlying medical diagnosis may guide inflammatory assessment in clinical settings. For some GLIM criteria, reliability is likely to be variable and dependent on the measure used. For example, determining muscle mass with anthropometry is less reliable than dual-energy absorptiometry, due to inter-observer error, especially for those untrained in performing anthropometry measurements [28]. The reliability of food intake assessment could be variable, depending on how intake is determined. As GLIM requires an understanding of recent food intake, a food diary or a 24 h recall (reflecting recent intake) is more appropriate than a food frequency questionnaire (reflecting intake over, for example, the past six months) [13]. At minimum, when conducting a validation study on GLIM criteria, authors should report how indicators were measured and the reliability of indicator determination.

In addition to the underlying reliability of the indicators used in GLIM, because of the nature of GLIM scoring, inter-rater reliability on categorization of malnutrition using GLIM criteria should also be determined. When reviewing the same patient data, would two clinicians/researchers/data extractors identify the same phenotypic and etiologic indicators as occurring or being triggered (yes/no)? To support this reliability, greater detail on what body composition measures should be used and the specific cut-points required for determining low muscle mass are needed. There is guidance in GLIM on the gastrointestinal conditions and symptoms that can lead to reduced assimilation of nutrients, as well as inflammatory diagnoses to consider as acute or chronic. However, the GLIM criteria require clinical judgement to determine severity of these conditions and whether the indicator is triggered. Guidance on intensity, frequency and duration of symptoms is needed to support inter-rater reliability.

Further, validity and reliability need to be established in diverse patient groups and sectors for GLIM to be used globally [22,27]; for example, it cannot be assumed that if GLIM is found to have criterion validity in hospital patients, that it would also be valid for community-based patients. The latter needs to be demonstrated in its own validation study.

3. Study design and considerations in validating GLIM and testing inter-rater reliability

An initial consideration in designing a validation study for GLIM is the determination of a criterion or constructs appropriate for comparison. Constructs should be theoretically related to the concept of malnutrition (e.g. quality of life). As previously noted, a gold standard for malnutrition is elusive, but the Mini Nutrition Assessment – Full Form (MNA-FF), Subjective Global Assessment (SGA) and Patient Generated SGA for oncology patients and/or comprehensive nutrition assessment by a trained clinician, have been identified to be relevant semi-gold criterions for validation studies [23,29]. Individual indicators of nutritional status such as biochemical parameters, anthropometry, or food intake are insufficient as criterions [18,23,29]. Similarly, combined scores of various tools assembled specifically for a validation study (and thus have unclear validity themselves) are inappropriate for GLIM validation studies [18,23]. Related to the identification of an appropriate criterion is the requirement that the GLIM criteria being tested are not embedded within the criterion being used to assess GLIM. This is considered criterion contamination or incorporation bias [18,20,22,23]. Assessors of nutritional status should be blinded to diagnostic GLIM criteria results. Finally, when a criterion has unknown reliability, two assessors, blinded to the results of the GLIM diagnostic criteria should evaluate participants on their nutritional status, and be blinded to each other's assessment [22].

Once the criterion or construct for comparison has been selected, the next step is to determine sample size. For retrospective studies, determining whether the available sample provides sufficient power to estimate statistics with sufficient precision can be determined with a back-calculation. Jones [22] provides guidance on sample size calculation for both construct and criterion validation studies. Participants in either a retrospective or prospective validation study should be included irrespective of their nutritional status, so as to not bias the results [22].

Since validation of the GLIM criteria can be tested by both retrospective and prospective studies, each study design has specific aspects to take into consideration. It is recommended that retrospective validation studies be based on at least one phenotypic and one etiologic GLIM criterion, and for prospective studies, all GLIM criteria be included. Such a strategy will support comparison on the prevalence of malnutrition using various combinations of diagnostic criteria as well as comparison of validity statistics [19]. Validation studies that are based on phenotypic indicators, but missing etiologic variables, or the other way around, are not considered sound validation studies, as they violate the underlying concept of GLIM that malnutrition diagnosis should be made on their combination. Also, use of a medical diagnosis that may impact assimilation of nutrients or cause inflammation *without a severity rating* (i.e., assuming that all patients with (for example) cancer will have inflammation, or all patients with Crohn's disease will have reduced assimilation), is insufficient for validation testing. In prospective studies, severity of disease needs to be measured in a reliable and valid manner. Further, the various indicators for severity of diagnosis and cut-points for muscle mass and inflammatory markers can be tested to determine which is best for use as GLIM criteria, with respect to sensitivity (SE) and specificity (SP). Machine learning uses algorithms and statistical models when a wealth of high quality data is available [30]. This method could be used to validate cut-off points.

A minimum data set for retrospective studies would be: health care setting; country and continent; demographics (sex, age, ethnicity); health characteristics; at least one phenotypic *and* one etiologic GLIM indicator with defined cut-points; valid and reliable measurement of a construct that is theoretically associated with malnutrition OR inclusion of a concurrent semi-gold standard criterion OR predictive health outcome (not concurrent with determination of GLIM criteria). When the gold-standard criterion has some subjective component (e.g., nutrition assessment) and has no

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determination of reliability (e.g., not assessed by more than one assessor for the test patient), this should be noted as a limitation of the validation. A sufficient sample size would be demonstrated using the appropriate methods for estimation for construct or criterion validity [22]. Ideally, reliability of measures used in GLIM and the construct for comparison are determined in the validation sample.

The minimum data set for prospective criterion validation studies includes: health care setting; country and continent; demographics (sex, age, ethnicity); health characteristics; determination of measures used in GLIM; inclusion of valid and reliable severity rating for assimilation of food and inflammatory diseases; a variety of muscle mass measures for comparison, especially for those considered less reliable and accurate (e.g., BIA, anthropometry); an in-depth assessment of nutritional status (or, less preferable, SGA or PG-SGA in oncology patients or MNA-FF), preferably completed by two assessors independently; and health outcomes that are relevant for prediction. Reliability testing of some GLIM indicators that lack precision (e.g., food intake) should also be considered. Where these design components are missing, this should be noted in the limitations of the study. Prospective studies provide an ideal opportunity to test a variety of cut-points for GLIM variables. The recommendations for validation studies of GLIM are summarized in Table 3.

3.1. Statistical analyses for reliability and validity of GLIM criteria

Inter-rater reliability for triggering GLIM indicators is recommended to support use of these operational criteria, as some components are subjective (e.g., severity of disease that causes inflammation). Each variable or indicator can be present or absent in the scoring of GLIM. As this is a dichotomous response, Kappa would be used to determine inter-rater reliability and agreement among raters. Kappa accounts for the chance event that agreement is observed [22]. Kappa could be calculated for each indicator as well as for the overall categorization of 'malnourished', using combinations of one phenotypic and one etiologic variable included in the study. Kappa that is >0.80 is substantial, whereas 0.61–0.80 is moderate [31]; any lower values bring into question the reliability of the GLIM criteria. The 95% confidence interval is as important and more informative than the Kappa value and should also be presented [22,31].

When various GLIM variables are considered in a single validation study, descriptive analyses demonstrating prevalence of malnutrition based on specific combinations of phenotypic and etiologic indicators should be completed. This could include not only the recommended one phentotypic and one etiologic indicator, but also other combinations, e.g., two phenotypic and one etiologic, or the same phenotypic indicator with another etiologic indicator, to test and refine GLIM. Again machine learning would help to identify all possible combinations in a data set for comparison to the gold standard (Fig. 1, [32]). Prevalence for these combinations of GLIM contrasted with the prevalence as determined by the gold standard used in the validation study would also be an important result to document.

Construct validity is based on the convergent association of GLIM with constructs that it should be associated with, if GLIM sufficiently identifies malnutrition. Comparative analyses are typically done to determine construct validity. For example, discriminant validity would be determined by comparing prevalence of malnutrition based on GLIM criteria in various health care sectors. Proportions that are identified with malnutrition could be contrasted using a z-test. Convergent validity is typically determined by association analyses. Is the GLIM categorization of malnutrition associated with health related outcomes, such as physical functioning or quality of life? These types of analyses have been done with the ESPEN definition of malnutrition [33]. Bivariate tests will determine this association (e.g., Chi square, ANOVA etc.). It is important to note that construct validity is only established with respect to the constructs with which GLIM is compared in these analyses [22]. Associations with various constructs (bivariate or mulitivariate) are insufficient for determining criterion validity. Associations simply indicate that one concept/measure coincides with another; it does not confirm the validity of the test measure for measuring a specific concept. With respect to predictive validity when a health outcome is being predicted, association analyses are commonly used. The variance (i.e., R^2) explained by GLIM would provide information on the relative importance of the GLIM categorization of malnutrition to the outcome, when adjusting for covariates. However, predictive multivariate analyses are specific for the sample on which they are conducted, and more than one study confirming GLIM to predict health outcomes with that population group (e.g., hospital patients) is needed. Covariates should include demographics, disease severity and other known predictors of the health outcome

Table 3
Recommendations for validation studies of GLIM criteria.

Type of Validation Study	GLIM Criteria	Validity Comparator	Minimum other data required
Retrospective validation studies: criterion or construct validity	*Measured* data including at least one phenotypic and at least one etiologic indicator	Semi-gold standard for malnutrition, preferably in-depth nutritional assessment by a trained professional; MNA-FF, SGA/PG-SGA; or malnutrition related health outcome, such as in-hospital complication or mortality; or a valid measurement of a construct that is known to be related to malnutrition	Health care setting; country and continent; demographics (sex, age, ethnicity); health characteristics
Prospective validation studies: criterion validity	*Measured* data of all phenotypic and etiologic indicators, preferably including a variety of muscle mass measurements for reasons of comparison, a clear description of measurements of inflammation and food-intake/assimilation assessment	Semi-gold standard for malnutrition, preferably in-depth nutritional assessment by a nutritionally trained professional, performed independently by two trained assessors; or MNA-FF, SGA/PG-SGA; and malnutrition-related health outcome, such as in-hospital complication or mortality	Health care setting; country and continent; demographics (sex, age, education level, ethnicity); health characteristics

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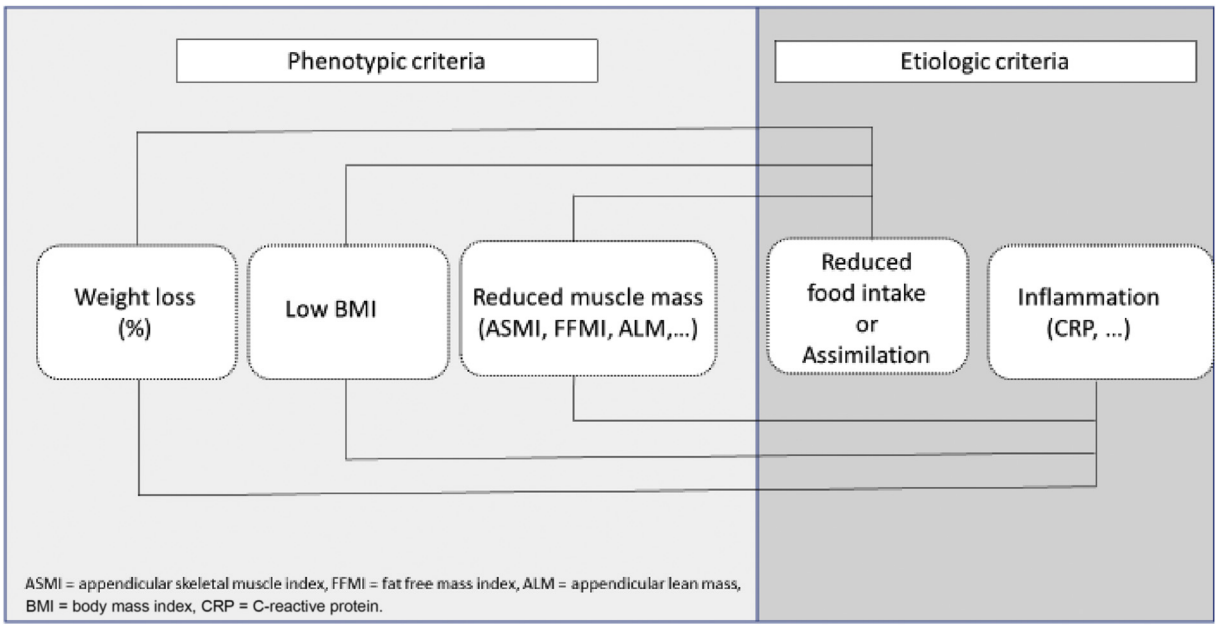

Fig. 1. Potential combinations of GLIM criteria for validation. ALM, appendicular lean mass; ASMI, appendicular skeletal muscle index; BMI, body mass index; CRP, C-reactive protein; FFMI, fat-free mass index; GLIM, Global Leadership Initiative on Malnutrition. Figure adapted with permission from Reference [32].

variable. Odds Ratios or Hazard Ratios can be applied to determine predictive validity in relation to outcome parameters such as mortality, length of stay or readmission.

The preferred statistical test for criterion validity is determination of SE and SP, as well as positive and negative predictive values (see Fig. 2). Receiver operating characteristic curves are not applicable as GLIM indicators are dichotomous (yes/no); however such analyses would be beneficial to confirm the cut-points used in GLIM variables (e.g., what % of weight loss is predictive of negative outcomes). If an outcome or criterion is numerical (e.g., length of stay, MNA score), a cut point to indicate worse/better status on the outcome will be needed to determine SE and SP. Published cut-points, or alternatively the median could be used to dichotomize the outcome variable. The simple equations below (Fig. 2) are used to determine SE and SP which can also be determined from the statistical output of a Chi square test.

In addition to SE and SP, positive (PPV) and negative (NPV) predictive value provide insight into the utility of the test measure. PPV and NPV are influenced by the true prevalence of the condition [34], and thus will vary depending on reference method, the study

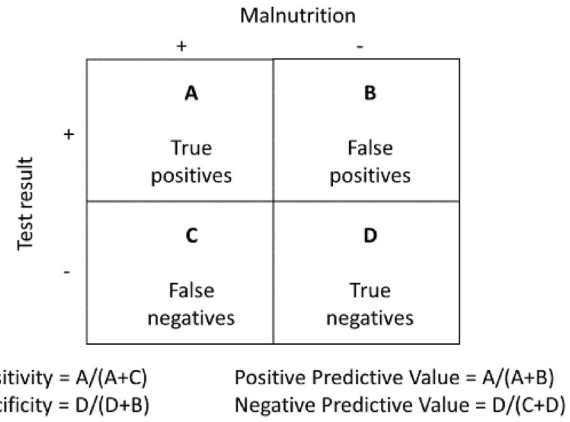

Fig. 2. Calculating sensitivity, specificity, positive predictive value, negative predictive value.

population and healthcare sector where GLIM is used. PPV and NPV provide insight into the utility of a measure considering this prevalence.

Although p-values also give an indication of statistical significance of a finding, for example when studying malnutrition in relation to mortality risk, p-values give no indication of the effect size, because p-values are also influenced by the sample size. Thus, we advise reporting coefficients, 95% confidence intervals, and p-values, as well as use of Cohen's d and Cramer's V for large samples [35]. Table 4 outlines accepted values for association and SE and SP when conducting construct and criterion validity respectively. Other common statistics recommended for outcomes and predictive validity are also provided.

3.2. Challenges for refinement of GLIM through future validation studies

The GLIM framework is not considered static. The GLIM criteria are unique in that they provide, for the first time, a world-wide consensus for categorizing malnutrition. It is however recognized that modifications may be expected with updated versions in the future. The original GLIM paper identifies some points that need to be worked on during the next few years. At least 21 possible combinations of parameters (at least one phenotypic and one etiologic criterion) can be used to categorize a patient as malnourished or not (Fig. 1), and it is of utmost interest to study which combination of parameters (and with which cut-points) GLIM meets its different goals of: identifying those who are malnourished, predicting outcomes associated with a poor nutritional status, and/or predicting those who will respond to nutritional interventions. Also, it may be important to identify which of the GLIM variables contributes most to malnutrition prevalence in different subgroups of patients. Based on the taxonomy of malnutrition features i.e. a) chronic disease or conditions with sustained inflammation, b) chronic disease with minimal or no perceived inflammation, c) acute disease or injury with severe inflammation, or d) pure chronic starvation not related to disease [3,5], it may well be that different combinations of etiologic and phenotypic

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Table 4
Recommended validation statistics.

Test Statistic	Type of Validity/Type of Variable	Recommended Interpretation
Sensitivity	Criterion- categorical variables	>80% required
Specificity	Criterion- categorical variables	>80% required
Chi square	Construct- categorical variables	$p < 0.05$ if sample size is < 200, $p < 0.01$ if sample size ≥200 and present 95% CI; large samples also use Cramers V (Φ_c)
T-test	Construct – GLIM categorical variable and construct numerical	$p < 0.05$ if sample size <200, $p < 0.01$ if sample size ≥200 and present 95% CI; samples also use Cohen's d (d)
Odd's/Hazard Ratio	Predictive validity- categorical health outcome variable	≥2.0 required
Z-test	Construct validity- discriminant, proportion identified as malnourished per GLIM	$p < 0.05$ if sample size <200, $p < 0.01$ if sample size ≥200 and 95% confidence intervals
	Reliability	
Kappa	Agreement	>0.8 required

indicators should be used for different forms of malnutrition or to achieve different goals. Responsiveness to a nutrition intervention may, for example, be different for patients who present with loss of body weight in combination with poor nutritional intake (reflecting starvation) compared with patients who also show low muscle mass and inflammation (reflecting disease related malnutrition with inflammation). On the other hand, predictive validity (for example 30-day mortality in acute hospitalized patients) may be better determined by one of the phenotypic variables (for example muscle parameters) in combination with inflammation.

Muscle mass is increasingly recognized as an important predictor of negative health outcomes and is now included in the GLIM diagnostic criteria. This is a great step forward as compared with previous operational definitions, which were mostly based on weight loss and BMI. The GLIM paper provides different options to identify a low muscle mass, whereby choices may depend on resources, time and availability for specific cut-points. For now this seems like the best way to move forward and to start using GLIM in practice. However, it is acknowledged that different ways to measure muscle mass provide different results. To give an example: in a cohort of patients with cancer undergoing three different measurements of muscle mass (by bioelectrical impedance, mid upper arm muscle circumference and CT scan analysis), the prevalence of low muscle mass varied from 13% (upper arm muscle circumference) to 93% (bioelectrical impedance) in the same cohort [36]. During the next few years, there will be opportunities to optimize the GLIM criteria by considering optimal cut-points for the different muscle mass measurements according to different ethnicities, taking into account the suggestions for good quality validation studies as described here. In addition, muscle quality (not yet incorporated in the GLIM) could be studied, as there is increasing evidence that not only muscle quantity, but also muscle quality [37] and strength [38] are associated with clinical outcomes. These are joint tasks with the sarcopenia community.

4. Conclusion and recommendations

The GLIM criteria for malnutrition are unique in that they, for the first time, provide a globally accepted starting point to categorizing patients as malnourished. This is going to aid our understanding of the magnitude of malnutrition across different continents and across different health care settings. For now, having this world-wide accepted diagnostic framework is a step forward and we encourage the use of this framework to show how GLIM can influence decision making and patient treatment and outcome. Reporting on this use will be important for understanding the utility of GLIM in practice. Meanwhile, validation studies are necessary to work towards refinement of the GLIM criteria. This paper provides guidance for performing good quality validation studies for nutrition measures overall, and GLIM in particular. We call for authors to publish these validation papers in leading clinical nutrition journals (e.g., JPEN, Clinical Nutrition, JAND). Submission of the protocols for these studies to the GLIM Working Group would help to track ongoing prospective studies. Next to individual studies, we recommend the building of a large database to merge data and to allow for determining cut-points of various measures upon which GLIM is based for different (sub)populations and health care settings to further support the refinement of the GLIM criteria.

Authorship statement

M. de van der Schueren and H. Keller equally contributed to the conception and design of the research and drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Financial disclosre

None declared.

Conflicts of interest

Authors are GLIM working group members.

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