Journal of Parenteral and Enteral Nutrition

GLIM criteria at hospital admission predict 8-year all-cause mortality in elderly patients with type 2 diabetes mellitus. Results from VIDA study.

Journal:	*Journal of Parenteral and Enteral Nutrition*
Manuscript ID	JPEN-2019-09-279.R2
Manuscript Type:	Original Communication
Date Submitted by the Author:	n/a
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Keywords:	Diabetes < Research and Diseases, malnourished, MNA-SF, survival, Kaplan-Meier
Abstract:	Background: Diabetes and older age are associated with an increased risk of malnutrition and mortality. Recently, the Global Leadership Initiative on Malnutrition (GLIM) provided a two-step approach for the malnutrition diagnosis based on phenotypic and etiologic criteria. In this study, we aimed to determine whether GLIM nutritional status at admission was associated with long term survival in elderly patients with type 2 diabetes. Additionally, we aimed to identify which GLIM criteria were more able to become prognostic indicators of early or late death. Methods: Our study included a convenience sample of 159 type 2 diabetic patients older than 65 years admitted to the internal medicine wards of different Spanish hospitals: the VIDA-survival cohort. Nutritional status was retrospectively assessed with the new GLIM criteria for the diagnosis of malnutrition. The main outcome was long-term mortality in the cohort during an 8-year follow-up. Bivariate tables summarized the variables of interest and Kaplan-Meier survival curves and adjusted Cox regressions were performed. Results: According to the GLIM criteria we observed that the 35.8% and 16.3% of the VIDA-survival cohort were categorized as having moderate and severe malnutrition, respectively. Severe malnutrition was associated with increased mortality (HR= 2.09, 95%CI=1.29-3.38),

	compared to non-malnourished participants. Moderate malnutrition had a neutral effect on all-cause mortality (HR= 1.30, 95%CI=0.88-1.92). Low plasma albumin, surrogate marker of inflammation, was strongly associated with early mortality. Conclusion: Our study provides evidence that severe malnutrition according to GLIM criteria is associated with increased long-term all-cause mortality among elderly individuals with type 2 diabetes

GLIM criteria at hospital admission predict 8-year all-cause mortality in elderly patients with type 2 diabetes mellitus. Results from VIDA study.

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Financial disclosures: None declared

Conflict of interest: None declared.

ABSTRACT

Background: Diabetes and older age are associated with an increased risk of malnutrition and mortality. Recently, the Global Leadership Initiative on Malnutrition (GLIM) provided a two-step approach for the malnutrition diagnosis based on phenotypic and etiologic criteria. In this study, we aimed to determine whether GLIM nutritional status at admission was associated with long term survival in elderly patients with type 2 diabetes. Additionally, we aimed to identify which GLIM criteria were more able to become prognostic indicators of early or late death.

Methods: Our study included a convenience sample of 159 type 2 diabetic patients older than 65 years admitted to the internal medicine wards of different Spanish hospitals: the VIDA-survival cohort. Nutritional status was retrospectively assessed with the new GLIM criteria for the diagnosis of malnutrition. The main outcome was long-term mortality in the cohort during an 8-year follow-up. Bivariate tables summarized the variables of interest and Kaplan-Meier survival curves and adjusted Cox regressions were performed.

Results: According to the GLIM criteria we observed that the 35.8% and 16.3% of the VIDA-survival cohort were categorized as having moderate and severe malnutrition, respectively. Severe malnutrition was associated with increased mortality (HR= 2.09, 95%CI=1.29-3.38), compared to non-malnourished participants. Moderate malnutrition had a neutral effect on all-cause mortality (HR= 1.30, 95%CI=0.88-1.92). Low plasma albumin, surrogate marker of inflammation, was strongly associated with early mortality.

Conclusion: Our study provides evidence that severe malnutrition according to GLIM criteria is associated with increased long-term all-cause mortality among elderly individuals with type 2 diabetes.

Keywords: diabetes, malnourished, MNA-SF, survival

Clinical Relevancy Statement: The Global Leadership Initiative on Malnutrition (GLIM) has provided a two-step approach for the malnutrition diagnosis based on phenotypic and etiologic criteria and called for validation studies in specific populations. Here we show that severe, but not moderate, malnutrition significantly increased all cause mortality in a multicentric cohort of elderly patients with type 2 diabetes hospitalized for a number of acute illnesses and followed for 8 years after discharge.

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health problem and its prevalence and associated complications rise with age. According to the 2017 report of the International Diabetes Federation, 425 million people worlwide (8.8 % of adults 20-79 years) are estimated to have T2DM and its prevalence more than doubles with age (~18% in individuals age 65 and older) [1]. Further, although all people with T2DM have an increased burden of disease, it is the elderly individuals with T2DM who suffer from a disproportionate increased risk of diabetes-associated complications and mortality [2]. This increased vulnerability leads to more hospitalizations and longer hospital stays for the elder compared to their younger diabetic counterparts [3]

Both diabetes and older age have been also associated with an increased risk for malnutrition. Compelling evidence shows impaired clinical outcomes and survival when T2DM is associated with a poor nutritional status [4]. Nevertheless, survival studies assessing the nutritional status in elderly patients with diabetes are scarce, despite of their increased fragility. This paucity of data is explained in part due to the lack of a consensus in a malnutrition diagnostic tool validated in populations with T2DM. It is, therefore, of paramount importance to produce such assessment tool to detect older individuals at risk with emphasis on those affected with T2DM so that this vulnerable population can benefit from early detection and interventions for malnutrition which can reduce mortality in those individuals.

Recently, the Global Leadership Initiative on Malnutrition (GLIM) provided a two-step approach to the malnutrition diagnosis based on phenotypic and etiologic criteria. As this novel consensus was released, the authors also called for validation studies and feedback [5] .

In this study, we examined the nutritional status and comorbidities at hospital admission in a multicenter cohort of elderly individuals with T2DM hospitalized for acute illnesses [6]. We aimed to determine whether GLIM criteria at admission was associated with survival outcomes in these

individuals during the subsequent 8-year follow-up. Additionally, we identified those criteria more amenable to become prognostic indicators of early or late death in this cohort.

Materials and methods

Sample and data collection

Data for this retrospective study were obtained from the case report forms (CRFs) pertaining to the VIDA study (n=1015) examining the prevalence of malnutrition in patients older than 65 years with T2DM admitted to the internal medicine wards of 35 Spanish hospitals. A detailed description of the design, methodology, sample size calculation, and development of the VIDA study is provided elsewhere [6,7]. Individuals were hospitalized for acute illnesses or with exacerbation of their chronic diseases. All cases were consecutively included between May 2007 and May 2008 and patients' first evaluation was carried out within 24-72 hours after hospital admission. All patients signed an informed consent form to participate in the study. The Clinical Research Ethics Committee (CREC) at Hospital Universitario La Paz (Madrid. Spain) approved the project.

The VIDA-survival cohort included 159 participants sampled from the VIDA study as a convenience sample with all individuals whose CRFs included information on follow-up and with no missing data on any of the variables necessary for categorization according to the GLIM criteria. All participants were followed as outpatients by their respective nutrition units. To assess potential selection bias, these 159 cases were compared with the complete VIDA cohort. Table 1 identifies those characteristics and comorbidities which might affect mortality in the two groups. Although the VIDA-survival cohort included a larger percentage of patients with diabetic neuropathy and retinopathy, the bivariate comparisons suggest and that the study sample is similar to the full VIDA cohort.

For this post-hoc analysis, participants were followed from the initial examination at hospital admission until they died or the end of December 2015. The main outcome of the study was long-term mortality in the VIDA-survival cohort during an 8-year follow-up. Vital status and date of death were established through linkage with the Spanish national death registry.

Nutritional status assessment

The new GLIM approach for the diagnosis of malnutrition is a 2 step process [5]. Previously, a validated risk screening tool was used to identify individuals 'at risk' of malnutrition. This initial screening was carried out with the MNA-SF [8]. Patients were categorized as having "normal nutritional status" (score ≥12), "at risk of malnutrition" (score between 8-11), or "malnourished" (score ≤7). Individuals in the two latter categories were considered 'at risk' according to the new GLIM criteria.

Those "at risk" individuals were considered malnourished if they met at least and simultaneously 1 phenotypic criterion and 1 etiologic criterion. The phenotypic criteria to be considered were: i) non-volitional weight loss: >5% within past 6 months, ii) low body mass index: <20 kg/m^2 if < 70 years, or <22 kg/m^2 if >70 years, and iii) reduced muscle mass: bed or chair bound subject or mid-arm < 21 cm or calf circumferences < 31 cm. Etiologic criteria were i) reduced food intake or assimilation: severe or moderate decrease in food intake during the past 3 months or those with any chronic GI condition that adversely impacted food assimilation or absorption, and ii) the presence of inflammation: plasma albumin in the lower quartile [9–12]. Information regarding food intake provided by patients was corroborated by their caregivers (usually a close relative) present during the hospitalization process.

The severity of malnutrition was determined based on three phenotypic criteria. Stage 1 or moderate malnutrition required at least 1 of the next phenotypic criterion: i) non-volitional weight loss (5–10% within the past 6 months), ii) low BMI: <20 kg/m^2 if < 70 years, or <22 kg/m^2 if >70 years, or iii) reduced muscle mass: either mid arm circumference < 21 cm or calf circumference < 31 cm. Stage 2 or severe Malnutrition. Severe Malnutrition required at least 1 of the next phenotypic criterion: i) non-volitional weight loss (>10% within the past 6 months), ii) low BMI: <18.5 kg/m^2 if < 70 years or <20 kg/m^2 if >70 years, or iii) reduced muscle mass: bed or chair bound subject or, alternatively, both mid arm circumference < 21 cm and calf circumference < 31 cm).

Statistical analysis

Bivariate tables summarized the variables of interest. Chi-square tests were used to test associations among categorical variables, while Student's t-test or Mann-Whitney U-test were used to compare continuous normal or non-normal data, respectively. The Cox univariate model was used to assess the relationship between overall survival and malnutrition categories according to the GLIM criteria. Multivariate models were also generated by adjusting by age and medical conditions (comorbidities) present at the time of admission. The results were expressed as Hazard ratios (ORs) and corresponding 95% confidence intervals (CIs). The assumption of proportionality was tested through the analysis of Schoenfeld residuals of the covariates introduced in the model. In survival models, probabilities of death and its modulation by GLIM categories over the follow-up period were calculated using Kaplan-Meier analysis. Data were analyzed using R version 3.1.3 (http://www.r-project.org) and the appropriate packages. Level of significance was set at 0.05.

Results

Prevalence of malnutrition in geriatric T2DM patients.

We used the recently developed GLIM criteria to diagnose malnutrition in 159 hospitalized patients with T2DM from the VIDA-survival cohort (Table 2). First, the MNA-SF was used to identify individuals 'at risk' of malnutrition. Patients categorized as "at risk of malnutrition" (score 8-11) or "malnourished" (score ≤7) were considered 'at risk' according to the new GLIM criteria. An impaired nutritional status was observed in 73% of the studied population with a balanced distribution between sexes (72.3% vs. 73.7% for men and women, respectively, p=0.985).

As the GLIM consensus is a two-step model, the diagnosis of malnutrition was conducted by assessing phenotypic and etiologic criteria in those "at risk" individuals according to MNA-SF. Among the phenotypic criteria, non-volitional weight loss, low BMI, and reduced muscle mass were met by the 54.7%, 14.6%, and 50% of the patients with T2DM, respectively. The etiologic criteria, namely reduced food intake or assimilation, and inflammation were observed in the 57.9% and 23.4% of the individuals, respectively. Overall, 52.9% of the VIDA-survival cohort was considered malnourished since they met at least 1 phenotypic criterion and 1 etiologic criterion. No sex-differences were observed either in the malnutrition diagnosis or in any of the criteria studied.

Finally, the severity of malnutrition was determined based on phenotypic criteria. We observed that the 35.8% and 16.3% of the VIDA-survival cohort were classified as having moderate and severe malnutrition, respectively, since they met at least one phenotypic criteria with the aggravated thresholds proposed by the GLIM consensus. Again, no differences were observed regarding the severity categories between men and women.

Death rate depends on malnutrition presence and severity during hospital admission in patients with T2DM.

During 599 person-years of follow-up, 130 deaths occurred with an incidence rate of 22/100 person-years. All individuals were between 65 and 93 years old. Table 3 shows the characteristics of the study population segmented by GLIM categories. Subjects with severe malnutrition had lower BMIs and plasma albumin at hospital admission compared with those non-malnourished or with moderate malnutrition. Individuals with moderate malnutrition were associated with decreased intake of oral antidiabetic medications. A lower incidence of cerebrovascular disease was also observed in non-malnourished individuals. Across the GLIM categories there were no differences in either sex distribution, age, smoking status or plasma values of cholesterol, glucose, and HbA1c at admission. Illnesses of the upper respiratory tract (pneumonia and respiratory failure) were the most frequent cause of admission, followed by heart failure and cerebrovascular disease (Table 3). However, apart from an increased incidence of heart failure among subjects with moderate malnutrition, there were no differences in the causes of hospitalization among the GLIM categories.

Survival according to GLIM categories was analyzed using Kaplan-Meier curves (Fig. 1).Higher mortality rates were observed in individuals with severe malnutrition, while longer survivals occurred among non-malnourished participants ($p<0.009$ for the log-rank test). The median survival was 3.5 years for non-malnourished subjects *versus* 1.9 and 0.7 years for moderate and severe malnourished, respectively.

Univariate Cox models confirmed that severe malnutrition was significantly associated with increased mortality (HR= 2.09, 95%CI=1.29-3.38, p=0.003), compared to non-malnourished participants (HR=1). Moderate malnutrition had a neutral effect on all-cause mortality among the elderly with T2DM (HR= 1.30, 95%CI=0.88-1.92, p=0.18). Interestingly, the association of severe malnutrition with all-cause mortality was maintained when age and comorbidity were added as covariate in an adjusted multivariate Cox analysis (HR= 1.96, 95%CI=1.20-3.20, p=0.007), as well as when age and cause of admission were introduced in the survival model (HR= 1.95, 95%CI=1.16-3.29, p=0.012).

Prognostic criteria of early and late death

According to the results described, the diagnosis of severe malnutrition during admission doubled the risk of death during 8 years of follow-up in elderly patients with T2DM . Next, we wondered if the risk of death due to malnutrition, as well as to the criteria that define malnutrition, would remain constant throughout the follow-up. For this we calculated the HRs at different times during the follow-up. According to the results shown in figure 2, the presence of moderate malnutrition does not increase the risk of death during the follow-up. On the other hand, severe malnutrition acts as a determinant of death throughout the follow-up. However, this factor produces a remarkable acute increase in mortality during the first year of follow-up (HRs ~ 3 at 3 months and at one year of follow-up) while a gradual decrease in its influence as a risk factor was observed during follow-up. (HRs ~ 2 from the 4th year).

When we studied separately the criteria that define malnutrition according to the GLIM consensus, we observed that non-volitional weight loss did not increase the risk of death at any intermediate point during the follow-up. On the contrary, the presence of a reduced BMI was consistently the most determining factor acting upon mortality throughout the follow-up (HRs ~ 3 during the 8 years). The presence of a reduced muscle mass and reduced food intake or assimilation did not increase acute mortality (at 3 months), but there was an effect on mortality from year 1 to the end of follow-up (HRs ~ 2 for both criteria after the first year). Finally, the presence of inflammation during admission tripled mortality in patients at 3 months of follow-up, although the importance of this factor was declining throughout the follow-up until it became insignificant at the seventh year of follow-up.

Discussion.

The high mortality and morbidity among older people with T2DM can be considered as a global public health concern. The GLIM consensus recently provided a new approach to the diagnosis of malnutrition and called for validation studies in specific populations [5]. Indeed, some recent studies have already shown the usefulness of this instrument to predict mortality in hospitalized patients with hematologic malignancies [13],and those undergoing abdominal resections [14]. As there is no evidence yet to support the suitability of this new tool in defining malnutrition in hospitalized geriatric patients with T2DM, we carried out this study to determine whether malnutrition, according to GLIM consensus, can predict mortality in those vulnerable individuals. To the best of our knowledge, this is the first longitudinal study investigating nutritional status and mortality during 8 years of follow-up in older people with T2DM. We found that severe, but not moderate, malnutrition significantly increased all-cause mortality in a multicenter cohort of elderly individuals with T2DM hospitalized for a number of acute illnesses and followed for 8 years after discharge.

The elderly population is the fastest growing demographic group worldwide [15]. Yet, older patient population is poorly represented in nutritional studies. This scarcity of data has clinical repercussions since older patients have an increased burden of comorbidities, geriatric syndromes, and physiological alterations compared to their younger counterparts. We had previously reported that malnutrition, according to the ESPEN definition, increased both the length of hospital stay and the odds of in-hospital death in the VIDA cohort [6]. Indeed, malnutrition was the only factor significantly associated with in-hospital mortality in our analysis of this T2DM cohort [6]. Additionally, mounting evidence shows that malnutrition, regardless of the criteria used to define it, is independently associated with a number of morbidities and mortality [16,17]. It should be noted that mortality may be influenced by other factors besides nutritional status alone, especially age, comorbidities, and cause of hospitalization. We found, however, that these confounding factors were distributed equally among the groups defined by the nutritional status in our cohort (non-malnourished, moderate and severe malnutrition), which

makes it unlikely that they were biasing the mortality rate toward any specific GLIM category. Moreover, we proved that the association of GLIM consensus and mortality remained after controlling for morbidity and the cause of admission.

Our results showed a much higher prevalence of malnutrition (52.9%) according to GLIM consensus compared to 35.2 % when we used the full MNA or 10.7% according to the ESPEN definition in the VIDA-survival cohort. Due to the novelty of the GLIM criteria, we have not been able to find any study comparing the prevalence of malnutrition with classic tools such as MNA or SGA versus GLIM. In addition, there are very few studies to investigate the prevalence of malnutrition in different populations using this tool. The malnutrition prevalence in the VIDA-survival cohort (52.9%), although elevated, seems to be in line with other reports from different populations using the GLIM definition of malnutrition; 64.8% in patients with oropharyngeal dysphagia after stroke [18], 35.4% among patients having gastrointestinal resections [14], 32% in patients with chronic liver disease [19], and 25.8% in hospitalized patients with hematologic malignancy [13]. This is somewhat expected as the literature shows a wide range of malnutrition prevalence according to the screening tools [20–23]. However, it should be highlighted that only those categorized with severe malnutrition (16.4%) were associated with increased risk of all-cause mortality. We hypothesize that moderate malnutrition might associate with other morbidities, but only severe malnutrition, which require a most stringent definition, associates with reduced survival in our elderly diabetic patients. Whether or not this is a specific trait of our cohort should be addressed in future investigations.

The GLIM consensus includes non-volitional weight loss among its phenotypic criteria, and this criterion was met by 54.7% of our cohort. Despite its well-known prognostic value [24,25], we did not find it associated with all cause mortality. People with T2DM have a higher BMI than subjects in the general population of the same age and sex [26]. Consequently, weight loss might go unnoticed in in routine check-ups and it may not be perceived as detrimental as the overweight/obese individuals with

T2DM have repeatedly been encouraged to lose weight. This phenomenon might also explain, at least partially, the dramatic increase in mortality in individuals with low BMI, since the required reduction in BMI to meet the low BMI criterion has to be greater in patients with T2DM whose BMIs were more likely of initially falling into the overweight/obese range. Indeed, reduced lean body mass doubled the mortality risk in our cohort from the first year of follow-up onwards. In spite of the dramatic association of BMI with reduced survival, we do not currently know whether this effect would be equally relevant to all categories of BMI. In this context we hypothesize that GLIM criteria have an added value over BMI alone as consider a number of conditions that can modulate (for better or worse) the effect of BMI on survival.

Loss of muscle mass leads to sarcopenia that contributes to frailty syndrome [27] and T2DM increases both prevalence and incidence of frailty in older adults [28]. In this study we used mid-arm and calf circumferences as indices of muscle mass to define moderate malnutrition. It should be noted that those parameters reflect both subcutaneous fat and body muscle mass. Differences in those measures should be interpreted with caution as they may indicate changes in either adipose or lean tissues. GLIM consensus considers these circumferences as "alternative measures" in spite of their limitations. The cutoffs values for muscle mass reduction were not adjusted for our population but rather we used the reference cutoffs previously validated for the MNA. This nutritional assessing tool is a widely employed as indicator of nutritional status in geriatric population [29] although it is not a gold standard method for muscle mass estimation.

GLIM consensus also factors in inflammation as surrogate marker of a number of comorbidities. Serum albumin is a negative acute phase protein[9] and many recent studies[10–12] have shown that concentrations of albumin, and other hepatic proteins such as transferrin and prealbumin, correlate with severity of the underlying disease, especially those that produce an inflammatory response. Likewise, medium or low-level inflammation is associated with a number of chronic diseases and may

exacerbate skeletal fragility in diabetes [30,31].In this regard, the The Academy of Nutrition and Dietetics, the American Society for Parenteral and Enteral Nutrition[32], and others [33,34]have stated that hepatic proteins are not indicators of nutritional status, but reflect severity of the inflammatory response and are indicators of morbidity, mortality, and recovery from acute and chronic diseases. The VIDA cohort was composed of individuals hospitalized for acute illnesses or with exacerbation of their chronic diseases. Some inflammatory component would be expected in both situations. Additionally, acute inflammation might be related to coexisting morbidities that can reduce early survival [35]. Not surprisingly this criterion was strongly associated with early mortality .Although the long-term predictive power of inflammation was somewhat reduced, it remained associated with mortality throughout the 8-year follow-up.

Our studied individuals share some specific characteristics; T2DM, old age, and hospitalization for acute illness. All these characteristics are independently associated with higher mortality rate. establishing a clear definition of malnutrition it is hence of the utmost importance in determining nutritional interventions and weight management in this population. In our analysis, the choice of a nutritional status was based on a mortality criterion and found a greater mortality risk only for those individuals with severe malnutrition according to GLIM criteria. Interestingly, this model performed equally well in predicting both acute deaths (those occurring 3 months after discharge) and deaths occurred at a time further from hospital admission, where nutritional status and other predictive variables were collected..

The main limitation of our study is the reduced number of participants, warranting further investigation in a larger cohort. Other limitations are the use of serum albumin as proxy measure of inflammation. Other inflammatory markers such as C-reactive protein would be meaningful to be included in future studies. Also that the assessment of food intake was based on subjective information, the unavailability of the cause of death, and the use of anthropometric values to to evaluate the reduction of muscle mass instead of body composition. Finally, we used a convenience

sample selected from the VIDA study, which may introduce a selection bias. As strengths it should be noted that this is a multicenter study able to reduce between-hospital cause of admission and in-hospital treatment variations. We also had access to information regarding confounding factors, such as concomitant diseases and medications, cause of admission and biochemical parameters during hospitalization. Lastly, the longitudinal analysis is able to reduce statistical type I error, compared to a cross-sectional study, thus lending some credit to a cause–effect relationship of severe malnutrition and all-cause mortality.

Overall, our study provides evidence that only severe malnutrition according to GLIM criteria is associated with increased all-cause mortality among among older people with T2DM and calls for early detection and interventions for malnutrition (i.e., oral nutritional supplements or dietary counseling) which may reduce mortality in those individuals.

Acknowledgments

The VIDA study was supported by a grant from Abbott Laboratories. This study has been funded by project PI17/02268 (Instituto de Salud Carlos III) and by Fondo Europeo de Desarrollo Regional (FEDER): "Una manera de hacer Europa". JMA-M is partially supported by a Miguel Servet fellowship (Instituto de Salud Carlos III) and by the DGA Group Biology of adipose tissue and metabolic complications (B03_17R), co-financed with the FEDER Aragón 2014-2020: "Construyendo Europa desde Aragón". We thank Prof. A. Beltran-Gila for her support and critical observations.

Statement of autorship.

AS-P, CG-C, AM-P, JMG-A, and RB-P designed the study and collected the data. AS-P, AS-A, and JMA-M analyzed the data. AS-P, SE, and JMA-M wrote the manuscript. All authors approved the final manuscript and take public responsibility for the content of the article.

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Table 1. Characteristics and comorbidities of the VIDA cohort and the mortality sub-cohort at hospital admission.

	VIDA	**VIDA-SURVIVAL**	**p**
	N=1015	*N=159*	
Women	510 (50.3%)	76 (47.8%)	0.617
Age (years)	77.9 (6.92)	78.1 (6.94)	0.797
MNA score	19.7 (5.22)	19.0 (6.25)	0.207
BMI (kg/m^2)	28.1 (8.08)	27.6 (6.19)	0.349
Smoking			
Yes	69 (6.87%)	15 (9.49%)	0.446
Ex	360 (35.9%)	58 (36.7%)	
No	575 (57.3%)	85 (53.8%)	
Pharmacological tratments			
Insulin	335 (33.0%)	53 (33.3%)	1.000
Oral Antidiabetic Drugs	701 (69.1%)	109 (68.6%)	0.970
Antihypertensive	774 (76.3%)	115 (72.3%)	0.330
Hypolipidemic	395 (38.9%)	55 (34.6%)	0.339
Anticoagulant	205 (20.2%)	34 (21.4%)	0.811
Antiplatelet	458 (45.1%)	82 (51.6%)	0.152
Comorbidities			
Diabetic nephropathy	182 (17.9%)	20 (12.6%)	0.121
Diabetic retinopathy	197 (19.4%)	64 (40.3%)	<0.001
Diabetic neuropathy	87 (8.57%)	33 (20.8%)	<0.001
Ischemic cardiomyopathy	282 (27.8%)	50 (31.4%)	0.390
Cerebrovascular disease	170 (16.7%)	24 (15.1%)	0.684

MNA: Mini Nutritional Assessment . BMI: Body Mass Index

Table 2. Prevalence rates of malnutrition in geriatric patients with type 2 diabetes according to the new GLIM consensus

GLIM criteria	ALL	MEN	WOMEN	p
	N=159	*N=83*	*N=76*	
At risk (MNA-SF)	116 (73.0%)	60 (72.3%)	56 (73.7%)	0.985
Phenotypic criteria				
Non-volitional weight loss	87 (54.7%)	50 (60.2%)	37 (48.7%)	0.193
Low BMI	23 (14.6%)	12 (14.5%)	11 (14.7%)	1.000
Reduced muscle mass	79 (50.0%)	36 (43.4%)	43 (57.3%)	0.111
≥1 phenotypic criteria	118 (75.2%)	61 (73.5%)	57 (77.0%)	0.744
Etiologic criteria				
Reduced food intake or assimilation	92 (57.9%)	47 (56.6%)	45 (59.2%)	0.866
Inflammation	36 (23.4%)	18 (22.8%)	18 (24.0%)	1.000
≥1 etiologic criteria	101 (65.6%)	48 (60.8%)	53 (70.7%)	0.261
Malnutrition	83 (52.9%)	42 (51.2%)	41 (54.7%)	0.785
Severity:				0.433
Moderate	57 (35.8%)	31 (37.3%)	26 (34.2%)	
Severe	26 (16.4%)	11 (13.3%)	15 (19.7%)	

Data are expressed as number and percentage of the VIDA-survival cohort.

MNA-SF: Mini Nutritional Assessment – Short Form. BMI: Body Mass Index

TABLE 3. Characteristics and comorbidities of the VIDA-SURVIVAL study population at hospital admission, based on the GLIM categories

	Non-malnourished	**Moderate Malnutrition**	**Severe Malnutrition**	**p.overall**
	N=74	*N=57*	*N=26*	
Women	34 (45.9%)	26 (45.6%)	15 (57.7%)	
Age (years)	77.0 (6.45)	78.8 (6.68)	80.2 (8.20)	0.083
Time since onset of diabetes				0.937
< 10 years	35 (47.3%)	27 (47.4%)	14 (53.8%)	
> 10 years	38 (51.4%)	30 (52.6%)	12 (46.2%)	
BMI (kg/m^2)	28.8 (5.46)	28.2 (6.15)	22.7 (5.52)	<0.001
Glucose (mg/dl)	173 (76.6)	183 (113)	184 (90.2)	0.807
HbA1c (%)	7.38 (1.38)	7.51 (1.63)	6.88 (1.27)	0.210
Cholesterol (mg/dl)	161 (37.0)	161 (45.2)	155 (34.7)	0.800
Albumin (g/dl)	3.15 (0.62)	2.99 (0.65)	2.45 (0.68)	<0.001
Smoking status				0.884
Yes	8 (10.8%)	4 (7.02%)	3 (12.0%)	
Ex	27 (36.5%)	20 (35.1%)	10 (40.0%)	
No	39 (52.7%)	33 (57.9%)	12 (48.0%)	
Pharmacological treatments				
Insulin	23 (31.1%)	24 (42.1%)	4 (15.4%)	0.051
Oral Antidiabetic Drugs	61 (82.4%)	28 (49.1%)	20 (76.9%)	<0.001
Antihypertensive	55 (74.3%)	44 (77.2%)	16 (61.5%)	0.314
Hypolipidemic	30 (40.5%)	17 (29.8%)	8 (30.8%)	0.392
Anticoagulant	18 (24.3%)	11 (19.3%)	4 (15.4%)	0.581
Antiplatelet	38 (51.4%)	29 (50.9%)	15 (57.7%)	0.829
Comorbidities				

Dyslipidemia	40 (54.1%)	25 (43.9%)	7 (26.9%)	0.054
Diabetic nephropathy	8 (10.8%)	6 (10.5%)	5 (19.2%)	0.484
Diabetic retinopathy	29 (39.2%)	22 (38.6%)	12 (46.2%)	0.788
Diabetic neuropathy	13 (17.6%)	12 (21.1%)	8 (30.8%)	0.364
Ischemic cardiomyopathy	21 (28.4%)	18 (31.6%)	10 (38.5%)	0.632
Cerebrovascular disease	6 (8.11%)	12 (21.1%)	6 (23.1%)	0.050
Causes of hospitalization				
Pneumonia/ Respiratory failure	26 (35.1%)	15 (26.3%)	6 (23.1%)	0.388
Heart failure	19 (25.7%)	25 (43.9%)	5 (19.2%)	0.030
Urinary tract infection	1 (1.35%)	4 (7.02%)	1 (3.85%)	0.218
Metabolic decompensation	7 (9.46%)	4 (7.02%)	0 (0.00%)	0.314
Cerebrovascular disease	8 (10.8%)	3 (5.26%)	5 (19.2%)	0.157
Coronary artery disease	1 (1.35%)	0 (0.00%)	0 (0.00%)	1.000
Peripheral artery disease	4 (5.41%)	1 (1.75%)	1 (3.85%)	0.551
Neurological Cognitive deterioration	2 (2.70%)	3 (5.26%)	0 (0.00%)	0.582
Acute gastroenteritis	6 (8.11%)	3 (5.26%)	4 (15.4%)	0.310
Neoplasia	4 (5.41%)	6 (10.5%)	3 (11.5%)	0.424
Constitutional syndrome	1 (1.35%)	3 (5.26%)	2 (7.69%)	0.178
Others	8 (10.8%)	7 (12.3%)	1 (3.85%)	0.568

BMI: Body Mass Index. HbA1c: Glycated hemoglobin

Figure 1. Kaplan-Meier Curves for the 8 year overall survival from date of hospital admission, by BMI category.

Figure 2. Changes in the ratio of hazard functions of patients meeting the following conditions vs. those not meeting the conditions (HR=1) over the 8-year follow-up and corresponding 95% confidence intervals. Severe and moderate malnutrition are compared vs. non-malnourished individuals.

GLIM criteria at hospital admission predict 8-year all-cause mortality in elderly patients with type 2 diabetes mellitus. Results from VIDA study.

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Financial disclosures: None declared

Conflict of interest: None declared.

ABSTRACT

Background: Diabetes and older age are associated with an increased risk of malnutrition and mortality. Recently, the Global Leadership Initiative on Malnutrition (GLIM) provided a two-step approach for the malnutrition diagnosis based on phenotypic and etiologic criteria. In this study, we aimed to determine whether GLIM nutritional status at admission was associated with long term survival in elderly patients with type 2 diabetes. Additionally, we aimed to identify which GLIM criteria were more able to become prognostic indicators of early or late death.

Methods: Our study included a convenience sample of 159 type 2 diabetic patients older than 65 years admitted to the internal medicine wards of different Spanish hospitals: the VIDA-survival cohort. Nutritional status was retrospectively assessed with the new GLIM criteria for the diagnosis of malnutrition. The main outcome was long-term mortality in the cohort during an 8-year follow-up. Bivariate tables summarized the variables of interest and Kaplan-Meier survival curves and adjusted Cox regressions were performed.

Results: According to the GLIM criteria we observed that the 35.8% and 16.3% of the VIDA-survival cohort were categorized as having moderate and severe malnutrition, respectively. Severe malnutrition was associated with increased mortality (HR= 2.09, 95%CI=1.29-3.38), compared to non-malnourished participants. Moderate malnutrition had a neutral effect on all-cause mortality (HR= 1.30, 95%CI=0.88-1.92). Low plasma albumin, surrogate marker of inflammation, was strongly associated with early mortality.

Conclusion: Our study provides evidence that severe malnutrition according to GLIM criteria is associated with increased long-term all-cause mortality among elderly individuals with type 2 diabetes.

Keywords: diabetes, malnourished, MNA-SF, survival

Clinical Relevancy Statement: The Global Leadership Initiative on Malnutrition (GLIM) has provided a two-step approach for the malnutrition diagnosis based on phenotypic and etiologic criteria and called for validation studies in specific populations. Here we show that severe, but not moderate, malnutrition significantly increased all cause mortality in a multicentric cohort of elderly patients with type 2 diabetes hospitalized for a number of acute illnesses and followed for 8 years after discharge.

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health problem and its prevalence and associated complications rise with age. According to the 2017 report of the International Diabetes Federation, 425 million people worlwide (8.8 % of adults 20-79 years) are estimated to have T2DM and its prevalence more than doubles with age (~18% in individuals age 65 and older) [1]. Further, although all people with T2DM have an increased burden of disease, it is the elderly individuals with T2DM who suffer from a disproportionate increased risk of diabetes-associated complications and mortality [2]. This increased vulnerability leads to more hospitalizations and longer hospital stays for the elder compared to their younger diabetic counterparts [3]

Both diabetes and older age have been also associated with an increased risk for malnutrition. Compelling evidence shows impaired clinical outcomes and survival when T2DM is associated with a poor nutritional status [4]. Nevertheless, survival studies assessing the nutritional status in elderly patients with diabetes are scarce, despite of their increased fragility. This paucity of data is explained in part due to the lack of a consensus in a malnutrition diagnostic tool validated in populations with T2DM. It is, therefore, of paramount importance to produce such assessment tool to detect older individuals at risk with emphasis on those affected with T2DM so that this vulnerable population can benefit from early detection and interventions for malnutrition which can reduce mortality in those individuals.

Recently, the Global Leadership Initiative on Malnutrition (GLIM) provided a two-step approach to the malnutrition diagnosis based on phenotypic and etiologic criteria. As this novel consensus was released, the authors also called for validation studies and feedback [5] .

In this study, we examined the nutritional status and comorbidities at hospital admission in a multicenter cohort of elderly individuals with T2DM hospitalized for acute illnesses [6]. We aimed to determine whether GLIM criteria at admission was associated with survival outcomes in these

individuals during the subsequent 8-year follow-up. Additionally, we identified those criteria more amenable to become prognostic indicators of early or late death in this cohort.

Materials and methods

Sample and data collection

Data for this retrospective study were obtained from the case report forms (CRFs) pertaining to the VIDA study (n=1015) examining the prevalence of malnutrition in patients older than 65 years with T2DM admitted to the internal medicine wards of 35 Spanish hospitals. A detailed description of the design, methodology, sample size calculation, and development of the VIDA study is provided elsewhere [6,7]. Individuals were hospitalized for acute illnesses or with exacerbation of their chronic diseases. All cases were consecutively included between May 2007 and May 2008 and patients' first evaluation was carried out within 24-72 hours after hospital admission. All patients signed an informed consent form to participate in the study. The Clinical Research Ethics Committee (CREC) at Hospital Universitario La Paz (Madrid. Spain) approved the project.

The VIDA-survival cohort included 159 participants sampled from the VIDA study as a convenience sample with all individuals whose CRFs included information on follow-up and with no missing data on any of the variables necessary for categorization according to the GLIM criteria. All participants were followed as outpatients by their respective nutrition units. To assess potential selection bias, these 159 cases were compared with the complete VIDA cohort. Table 1 identifies those characteristics and comorbidities which might affect mortality in the two groups. Although the VIDA-survival cohort included a larger percentage of patients with diabetic neuropathy and retinopathy, the bivariate comparisons suggest and that the study sample is similar to the full VIDA cohort.

For this post-hoc analysis, participants were followed from the initial examination at hospital admission until they died or the end of December 2015. The main outcome of the study was long-term mortality in the VIDA-survival cohort during an 8-year follow-up. Vital status and date of death were established through linkage with the Spanish national death registry.

Nutritional status assessment

The new GLIM approach for the diagnosis of malnutrition is a 2 step process [5]. Previously, a validated risk screening tool was used to identify individuals 'at risk' of malnutrition. This initial screening was carried out with the MNA-SF [8]. Patients were categorized as having "normal nutritional status" (score ≥12), "at risk of malnutrition" (score between 8-11), or "malnourished" (score ≤7). Individuals in the two latter categories were considered 'at risk' according to the new GLIM criteria.

Those "at risk" individuals were considered malnourished if they met at least and simultaneously 1 phenotypic criterion and 1 etiologic criterion. The phenotypic criteria to be considered were: i) non-volitional weight loss: >5% within past 6 months, ii) low body mass index: <20 kg/m^2 if < 70 years, or <22 kg/m^2 if >70 years, and iii) reduced muscle mass: bed or chair bound subject or mid-arm < 21 cm or calf circumferences < 31 cm. Etiologic criteria were i) reduced food intake or assimilation: severe or moderate decrease in food intake during the past 3 months or those with any chronic GI condition that adversely impacted food assimilation or absorption, and ii) the presence of inflammation: plasma albumin in the lower quartile [9–12]. Information regarding food intake provided by patients was corroborated by their caregivers (usually a close relative) present during the hospitalization process.

The severity of malnutrition was determined based on three phenotypic criteria. Stage 1 or moderate malnutrition required at least 1 of the next phenotypic criterion: i) non-volitional weight loss (5–10% within the past 6 months), ii) low BMI: <20 kg/m^2 if < 70 years, or <22 kg/m^2 if >70 years, or iii) reduced muscle mass: either mid arm circumference < 21 cm or calf circumference < 31 cm. Stage 2 or severe Malnutrition. Severe Malnutrition required at least 1 of the next phenotypic criterion: i) non-volitional weight loss (>10% within the past 6 months), ii) low BMI: <18.5 kg/m^2 if < 70 years or <20 kg/m^2 if >70 years, or iii) reduced muscle mass: bed or chair bound subject or, alternatively, both mid arm circumference < 21 cm and calf circumference < 31 cm).

Statistical analysis

Bivariate tables summarized the variables of interest. Chi-square tests were used to test associations among categorical variables, while Student's t-test or Mann-Whitney U-test were used to compare continuous normal or non-normal data, respectively. The Cox univariate model was used to assess the relationship between overall survival and malnutrition categories according to the GLIM criteria. Multivariate models were also generated by adjusting by age and medical conditions (comorbidities) present at the time of admission. The results were expressed as Hazard ratios (ORs) and corresponding 95% confidence intervals (CIs). The assumption of proportionality was tested through the analysis of Schoenfeld residuals of the covariates introduced in the model. In survival models, probabilities of death and its modulation by GLIM categories over the follow-up period were calculated using Kaplan-Meier analysis. Data were analyzed using R version 3.1.3 (http://www.r-project.org) and the appropriate packages. Level of significance was set at 0.05.

Results

Prevalence of malnutrition in geriatric T2DM patients.

We used the recently developed GLIM criteria to diagnose malnutrition in 159 hospitalized patients with T2DM from the VIDA-survival cohort (Table 2). First, the MNA-SF was used to identify individuals 'at risk' of malnutrition. Patients categorized as "at risk of malnutrition" (score 8-11) or "malnourished" (score ≤7) were considered 'at risk' according to the new GLIM criteria. An impaired nutritional status was observed in 73% of the studied population with a balanced distribution between sexes (72.3% vs. 73.7% for men and women, respectively, p=0.985).

As the GLIM consensus is a two-step model, the diagnosis of malnutrition was conducted by assessing phenotypic and etiologic criteria in those "at risk" individuals according to MNA-SF. Among the phenotypic criteria, non-volitional weight loss, low BMI, and reduced muscle mass were met by the 54.7%, 14.6%, and 50% of the patients with T2DM, respectively. The etiologic criteria, namely reduced food intake or assimilation, and inflammation were observed in the 57.9% and 23.4% of the individuals, respectively. Overall, 52.9% of the VIDA-survival cohort was considered malnourished since they met at least 1 phenotypic criterion and 1 etiologic criterion. No sex-differences were observed either in the malnutrition diagnosis or in any of the criteria studied.

Finally, the severity of malnutrition was determined based on phenotypic criteria. We observed that the 35.8% and 16.3% of the VIDA-survival cohort were classified as having moderate and severe malnutrition, respectively, since they met at least one phenotypic criteria with the aggravated thresholds proposed by the GLIM consensus. Again, no differences were observed regarding the severity categories between men and women.

Death rate depends on malnutrition presence and severity during hospital admission in patients with T2DM.

During 599 person-years of follow-up, 130 deaths occurred with an incidence rate of 22/100 person-years. All individuals were between 65 and 93 years old. Table 3 shows the characteristics of the study population segmented by GLIM categories. Subjects with severe malnutrition had lower BMIs and plasma albumin at hospital admission compared with those non-malnourished or with moderate malnutrition. Individuals with moderate malnutrition were associated with decreased intake of oral antidiabetic medications. A lower incidence of cerebrovascular disease was also observed in non-malnourished individuals. Across the GLIM categories there were no differences in either sex distribution, age, smoking status or plasma values of cholesterol, glucose, and HbA1c at admission. Illnesses of the upper respiratory tract (pneumonia and respiratory failure) were the most frequent cause of admission, followed by heart failure and cerebrovascular disease (Table 3). However, apart from an increased incidence of heart failure among subjects with moderate malnutrition, there were no differences in the causes of hospitalization among the GLIM categories.

Survival according to GLIM categories was analyzed using Kaplan-Meier curves (Fig. 1).Higher mortality rates were observed in individuals with severe malnutrition, while longer survivals occurred among non-malnourished participants ($p<0.009$ for the log-rank test). The median survival was 3.5 years for non-malnourished subjects *versus* 1.9 and 0.7 years for moderate and severe malnourished, respectively.

Univariate Cox models confirmed that severe malnutrition was significantly associated with increased mortality (HR= 2.09, 95%CI=1.29-3.38, p=0.003), compared to non-malnourished participants (HR=1). Moderate malnutrition had a neutral effect on all-cause mortality among the elderly with T2DM (HR= 1.30, 95%CI=0.88-1.92, p=0.18). Interestingly, the association of severe malnutrition with all-cause mortality was maintained when age and comorbidity were added as covariate in an adjusted multivariate Cox analysis (HR= 1.96, 95%CI=1.20-3.20, p=0.007), as well as when age and cause of admission were introduced in the survival model (HR= 1.95, 95%CI=1.16-3.29, p=0.012).

Prognostic criteria of early and late death

According to the results described, the diagnosis of severe malnutrition during admission doubled the risk of death during 8 years of follow-up in elderly patients with T2DM . Next, we wondered if the risk of death due to malnutrition, as well as to the criteria that define malnutrition, would remain constant throughout the follow-up. For this we calculated the HRs at different times during the follow-up. According to the results shown in figure 2, the presence of moderate malnutrition does not increase the risk of death during the follow-up. On the other hand, severe malnutrition acts as a determinant of death throughout the follow-up. However, this factor produces a remarkable acute increase in mortality during the first year of follow-up (HRs ~ 3 at 3 months and at one year of follow-up) while a gradual decrease in its influence as a risk factor was observed during follow-up. (HRs ~ 2 from the 4th year).

When we studied separately the criteria that define malnutrition according to the GLIM consensus, we observed that non-volitional weight loss did not increase the risk of death at any intermediate point during the follow-up. On the contrary, the presence of a reduced BMI was consistently the most determining factor acting upon mortality throughout the follow-up (HRs ~ 3 during the 8 years). The presence of a reduced muscle mass and reduced food intake or assimilation did not increase acute mortality (at 3 months), but there was an effect on mortality from year 1 to the end of follow-up (HRs ~ 2 for both criteria after the first year). Finally, the presence of inflammation during admission tripled mortality in patients at 3 months of follow-up, although the importance of this factor was declining throughout the follow-up until it became insignificant at the seventh year of follow-up.

Discussion.

The high mortality and morbidity among older people with T2DM can be considered as a global public health concern. The GLIM consensus recently provided a new approach to the diagnosis of malnutrition and called for validation studies in specific populations [5]. Indeed, some recent studies have already shown the usefulness of this instrument to predict mortality in hospitalized patients with hematologic malignancies [13],and those undergoing abdominal resections [14]. As there is no evidence yet to support the suitability of this new tool in defining malnutrition in hospitalized geriatric patients with T2DM, we carried out this study to determine whether malnutrition, according to GLIM consensus, can predict mortality in those vulnerable individuals. To the best of our knowledge, this is the first longitudinal study investigating nutritional status and mortality during 8 years of follow-up in older people with T2DM. We found that severe, but not moderate, malnutrition significantly increased all-cause mortality in a multicenter cohort of elderly individuals with T2DM hospitalized for a number of acute illnesses and followed for 8 years after discharge.

The elderly population is the fastest growing demographic group worldwide [15]. Yet, older patient population is poorly represented in nutritional studies. This scarcity of data has clinical repercussions since older patients have an increased burden of comorbidities, geriatric syndromes, and physiological alterations compared to their younger counterparts. We had previously reported that malnutrition, according to the ESPEN definition, increased both the length of hospital stay and the odds of in-hospital death in the VIDA cohort [6]. Indeed, malnutrition was the only factor significantly associated with in-hospital mortality in our analysis of this T2DM cohort [6]. Additionally, mounting evidence shows that malnutrition, regardless of the criteria used to define it, is independently associated with a number of morbidities and mortality [16,17]. It should be noted that mortality may be influenced by other factors besides nutritional status alone, especially age, comorbidities, and cause of hospitalization. We found, however, that these confounding factors were distributed equally among the groups defined by the nutritional status in our cohort (non-malnourished, moderate and severe malnutrition), which

makes it unlikely that they were biasing the mortality rate toward any specific GLIM category. Moreover, we proved that the association of GLIM consensus and mortality remained after controlling for morbidity and the cause of admission.

Our results showed a much higher prevalence of malnutrition (52.9%) according to GLIM consensus compared to 35.2 % when we used the full MNA or 10.7% according to the ESPEN definition in the VIDA-survival cohort. Due to the novelty of the GLIM criteria, we have not been able to find any study comparing the prevalence of malnutrition with classic tools such as MNA or SGA versus GLIM. In addition, there are very few studies to investigate the prevalence of malnutrition in different populations using this tool. The malnutrition prevalence in the VIDA-survival cohort (52.9%), although elevated, seems to be in line with other reports from different populations using the GLIM definition of malnutrition; 64.8% in patients with oropharyngeal dysphagia after stroke [18], 35.4% among patients having gastrointestinal resections [14], 32% in patients with chronic liver disease [19], and 25.8% in hospitalized patients with hematologic malignancy [13]. This is somewhat expected as the literature shows a wide range of malnutrition prevalence according to the screening tools [20–23]. However, it should be highlighted that only those categorized with severe malnutrition (16.4%) were associated with increased risk of all-cause mortality. We hypothesize that moderate malnutrition might associate with other morbidities, but only severe malnutrition, which require a most stringent definition, associates with reduced survival in our elderly diabetic patients. Whether or not this is a specific trait of our cohort should be addressed in future investigations.

The GLIM consensus includes non-volitional weight loss among its phenotypic criteria, and this criterion was met by 54.7% of our cohort. Despite its well-known prognostic value [24,25], we did not find it associated with all cause mortality. People with T2DM have a higher BMI than subjects in the general population of the same age and sex [26]. Consequently, weight loss might go unnoticed in in routine check-ups and it may not be perceived as detrimental as the overweight/obese individuals with

T2DM have repeatedly been encouraged to lose weight. This phenomenon might also explain, at least partially, the dramatic increase in mortality in individuals with low BMI, since the required reduction in BMI to meet the low BMI criterion has to be greater in patients with T2DM whose BMIs were more likely of initially falling into the overweight/obese range. Indeed, reduced lean body mass doubled the mortality risk in our cohort from the first year of follow-up onwards. In spite of the dramatic association of BMI with reduced survival, we do not currently know whether this effect would be equally relevant to all categories of BMI. In this context we hypothesize that GLIM criteria have an added value over BMI alone as consider a number of conditions that can modulate (for better or worse) the effect of BMI on survival.

Loss of muscle mass leads to sarcopenia that contributes to frailty syndrome [27] and T2DM increases both prevalence and incidence of frailty in older adults [28]. In this study we used mid-arm and calf circumferences as indices of muscle mass to define moderate malnutrition. It should be noted that those parameters reflect both subcutaneous fat and body muscle mass. Differences in those measures should be interpreted with caution as they may indicate changes in either adipose or lean tissues. GLIM consensus considers these circumferences as "alternative measures" in spite of their limitations. The cutoffs values for muscle mass reduction were not adjusted for our population but rather we used the reference cutoffs previously validated for the MNA. This nutritional assessing tool is a widely employed as indicator of nutritional status in geriatric population [29] although it is not a gold standard method for muscle mass estimation.

GLIM consensus also factors in inflammation as surrogate marker of a number of comorbidities. Serum albumin is a negative acute phase protein[9] and many recent studies[10–12] have shown that concentrations of albumin, and other hepatic proteins such as transferrin and prealbumin, correlate with severity of the underlying disease, especially those that produce an inflammatory response. Likewise, medium or low-level inflammation is associated with a number of chronic diseases and may

exacerbate skeletal fragility in diabetes [30,31].In this regard, the The Academy of Nutrition and Dietetics, the American Society for Parenteral and Enteral Nutrition[32], and others [33,34]have stated that hepatic proteins are not indicators of nutritional status, but reflect severity of the inflammatory response and are indicators of morbidity, mortality, and recovery from acute and chronic diseases. The VIDA cohort was composed of individuals hospitalized for acute illnesses or with exacerbation of their chronic diseases. Some inflammatory component would be expected in both situations. Additionally, acute inflammation might be related to coexisting morbidities that can reduce early survival [35]. Not surprisingly this criterion was strongly associated with early mortality .Although the long-term predictive power of inflammation was somewhat reduced, it remained associated with mortality throughout the 8-year follow-up.

Our studied individuals share some specific characteristics; T2DM, old age, and hospitalization for acute illness. All these characteristics are independently associated with higher mortality rate. establishing a clear definition of malnutrition it is hence of the utmost importance in determining nutritional interventions and weight management in this population. In our analysis, the choice of a nutritional status was based on a mortality criterion and found a greater mortality risk only for those individuals with severe malnutrition according to GLIM criteria. Interestingly, this model performed equally well in predicting both acute deaths (those occurring 3 months after discharge) and deaths occurred at a time further from hospital admission, where nutritional status and other predictive variables were collected..

The main limitation of our study is the reduced number of participants, warranting further investigation in a larger cohort. Other limitations are the use of serum albumin as proxy measure of inflammation. Other inflammatory markers such as C-reactive protein would be meaningful to be included in future studies. Also that the assessment of food intake was based on subjective information, the unavailability of the cause of death, and the use of anthropometric values to to evaluate the reduction of muscle mass instead of body composition. Finally, we used a convenience

sample selected from the VIDA study, which may introduce a selection bias. As strengths it should be noted that this is a multicenter study able to reduce between-hospital cause of admission and in-hospital treatment variations. We also had access to information regarding confounding factors, such as concomitant diseases and medications, cause of admission and biochemical parameters during hospitalization. Lastly, the longitudinal analysis is able to reduce statistical type I error, compared to a cross-sectional study, thus lending some credit to a cause–effect relationship of severe malnutrition and all-cause mortality.

Overall, our study provides evidence that only severe malnutrition according to GLIM criteria is associated with increased all-cause mortality among among older people with T2DM and calls for early detection and interventions for malnutrition (i.e., oral nutritional supplements or dietary counseling) which may reduce mortality in those individuals.

Acknowledgments

The VIDA study was supported by a grant from Abbott Laboratories. This study has been funded by project PI17/02268 (Instituto de Salud Carlos III) and by Fondo Europeo de Desarrollo Regional (FEDER): "Una manera de hacer Europa". JMA-M is partially supported by a Miguel Servet fellowship (Instituto de Salud Carlos III) and by the DGA Group Biology of adipose tissue and metabolic complications (B03_17R), co-financed with the FEDER Aragón 2014-2020: "Construyendo Europa desde Aragón". We thank Prof. A. Beltran-Gila for her support and critical observations.

Statement of autorship.

AS-P, CG-C, AM-P, JMG-A, and RB-P designed the study and collected the data. AS-P, AS-A, and JMA-M analyzed the data. AS-P, SE, and JMA-M wrote the manuscript. All authors approved the final manuscript and take public responsibility for the content of the article.

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Table 1. Characteristics and comorbidities of the VIDA cohort and the mortality sub-cohort at hospital admission.

	VIDA	**VIDA-SURVIVAL**	**p**
	N=1015	*N=159*	
Women	510 (50.3%)	76 (47.8%)	0.617
Age (years)	77.9 (6.92)	78.1 (6.94)	0.797
MNA score	19.7 (5.22)	19.0 (6.25)	0.207
BMI (kg/m^2)	28.1 (8.08)	27.6 (6.19)	0.349
Smoking			
Yes	69 (6.87%)	15 (9.49%)	0.446
Ex	360 (35.9%)	58 (36.7%)	
No	575 (57.3%)	85 (53.8%)	
Pharmacological tratments			
Insulin	335 (33.0%)	53 (33.3%)	1.000
Oral Antidiabetic Drugs	701 (69.1%)	109 (68.6%)	0.970
Antihypertensive	774 (76.3%)	115 (72.3%)	0.330
Hypolipidemic	395 (38.9%)	55 (34.6%)	0.339
Anticoagulant	205 (20.2%)	34 (21.4%)	0.811
Antiplatelet	458 (45.1%)	82 (51.6%)	0.152
Comorbidities			
Diabetic nephropathy	182 (17.9%)	20 (12.6%)	0.121
Diabetic retinopathy	197 (19.4%)	64 (40.3%)	<0.001
Diabetic neuropathy	87 (8.57%)	33 (20.8%)	<0.001
Ischemic cardiomyopathy	282 (27.8%)	50 (31.4%)	0.390
Cerebrovascular disease	170 (16.7%)	24 (15.1%)	0.684

MNA: Mini Nutritional Assessment . BMI: Body Mass Index

Table 2. Prevalence rates of malnutrition in geriatric patients with type 2 diabetes according to the new GLIM consensus

GLIM criteria	**ALL**	**MEN**	**WOMEN**	**p**
	N=159	*N=83*	*N=76*	
At risk (MNA-SF)	116 (73.0%)	60 (72.3%)	56 (73.7%)	0.985
Phenotypic criteria				
Non-volitional weight loss	87 (54.7%)	50 (60.2%)	37 (48.7%)	0.193
Low BMI	23 (14.6%)	12 (14.5%)	11 (14.7%)	1.000
Reduced muscle mass	79 (50.0%)	36 (43.4%)	43 (57.3%)	0.111
≥1 phenotypic criteria	118 (75.2%)	61 (73.5%)	57 (77.0%)	0.744
Etiologic criteria				
Reduced food intake or assimilation	92 (57.9%)	47 (56.6%)	45 (59.2%)	0.866
Inflammation	36 (23.4%)	18 (22.8%)	18 (24.0%)	1.000
≥1 etiologic criteria	101 (65.6%)	48 (60.8%)	53 (70.7%)	0.261
Malnutrition	83 (52.9%)	42 (51.2%)	41 (54.7%)	0.785
Severity:				0.433
Moderate	57 (35.8%)	31 (37.3%)	26 (34.2%)	
Severe	26 (16.4%)	11 (13.3%)	15 (19.7%)	

Data are expressed as number and percentage of the VIDA-survival cohort.

MNA-SF: Mini Nutritional Assessment – Short Form. BMI: Body Mass Index

TABLE 3. Characteristics and comorbidities of the VIDA-SURVIVAL study population at hospital admission, based on the GLIM categories

	Non-malnourished	**Moderate Malnutrition**	**Severe Malnutrition**	**p.overall**
	N=74	*N=57*	*N=26*	
Women	34 (45.9%)	26 (45.6%)	15 (57.7%)	
Age (years)	77.0 (6.45)	78.8 (6.68)	80.2 (8.20)	0.083
Time since onset of diabetes				0.937
< 10 years	35 (47.3%)	27 (47.4%)	14 (53.8%)	
> 10 years	38 (51.4%)	30 (52.6%)	12 (46.2%)	
BMI (kg/m^2)	28.8 (5.46)	28.2 (6.15)	22.7 (5.52)	<0.001
Glucose (mg/dl)	173 (76.6)	183 (113)	184 (90.2)	0.807
HbA1c (%)	7.38 (1.38)	7.51 (1.63)	6.88 (1.27)	0.210
Cholesterol (mg/dl)	161 (37.0)	161 (45.2)	155 (34.7)	0.800
Albumin (g/dl)	3.15 (0.62)	2.99 (0.65)	2.45 (0.68)	<0.001
Smoking status				0.884
Yes	8 (10.8%)	4 (7.02%)	3 (12.0%)	
Ex	27 (36.5%)	20 (35.1%)	10 (40.0%)	
No	39 (52.7%)	33 (57.9%)	12 (48.0%)	
Pharmacological treatments				
Insulin	23 (31.1%)	24 (42.1%)	4 (15.4%)	0.051
Oral Antidiabetic Drugs	61 (82.4%)	28 (49.1%)	20 (76.9%)	<0.001
Antihypertensive	55 (74.3%)	44 (77.2%)	16 (61.5%)	0.314
Hypolipidemic	30 (40.5%)	17 (29.8%)	8 (30.8%)	0.392
Anticoagulant	18 (24.3%)	11 (19.3%)	4 (15.4%)	0.581
Antiplatelet	38 (51.4%)	29 (50.9%)	15 (57.7%)	0.829
Comorbidities				

Dyslipidemia	40 (54.1%)	25 (43.9%)	7 (26.9%)	0.054
Diabetic nephropathy	8 (10.8%)	6 (10.5%)	5 (19.2%)	0.484
Diabetic retinopathy	29 (39.2%)	22 (38.6%)	12 (46.2%)	0.788
Diabetic neuropathy	13 (17.6%)	12 (21.1%)	8 (30.8%)	0.364
Ischemic cardiomyopathy	21 (28.4%)	18 (31.6%)	10 (38.5%)	0.632
Cerebrovascular disease	6 (8.11%)	12 (21.1%)	6 (23.1%)	0.050
Causes of hospitalization				
Pneumonia/ Respiratory failure	26 (35.1%)	15 (26.3%)	6 (23.1%)	0.388
Heart failure	19 (25.7%)	25 (43.9%)	5 (19.2%)	0.030
Urinary tract infection	1 (1.35%)	4 (7.02%)	1 (3.85%)	0.218
Metabolic decompensation	7 (9.46%)	4 (7.02%)	0 (0.00%)	0.314
Cerebrovascular disease	8 (10.8%)	3 (5.26%)	5 (19.2%)	0.157
Coronary artery disease	1 (1.35%)	0 (0.00%)	0 (0.00%)	1.000
Peripheral artery disease	4 (5.41%)	1 (1.75%)	1 (3.85%)	0.551
Neurological Cognitive deterioration	2 (2.70%)	3 (5.26%)	0 (0.00%)	0.582
Acute gastroenteritis	6 (8.11%)	3 (5.26%)	4 (15.4%)	0.310
Neoplasia	4 (5.41%)	6 (10.5%)	3 (11.5%)	0.424
Constitutional syndrome	1 (1.35%)	3 (5.26%)	2 (7.69%)	0.178
Others	8 (10.8%)	7 (12.3%)	1 (3.85%)	0.568

BMI: Body Mass Index. HbA1c: Glycated hemoglobin

Figure 1. Kaplan-Meier Curves for the 8 year overall survival from date of hospital admission, by BMI category.

Figure 2. Changes in the ratio of hazard functions of patients meeting the following conditions vs. those not meeting the conditions (HR=1) over the 8-year follow-up and corresponding 95% confidence intervals. Severe and moderate malnutrition are compared vs. non-malnourished individuals.

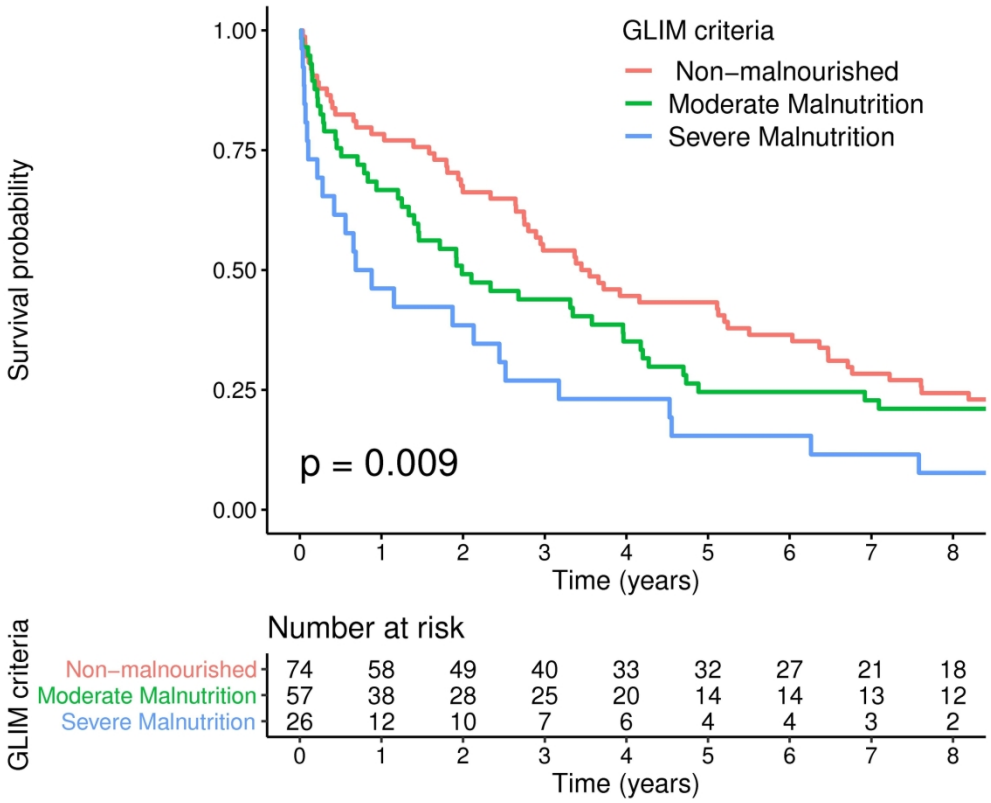
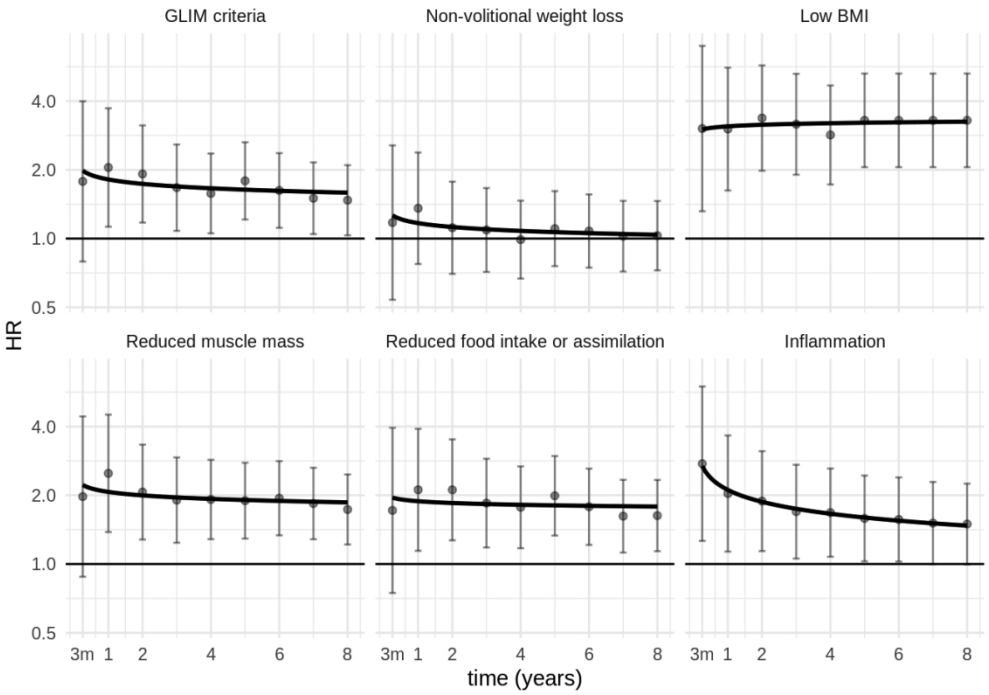


Figure 1

186x151mm (300 x 300 DPI)



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