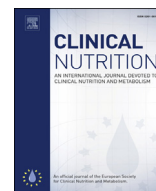




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Original article

The GLIM criteria as an effective tool for nutrition assessment and survival prediction in older adult cancer patients

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SUMMARY

Background & aims: Elderly cancer patients are at particularly high risk for malnutrition because both the disease and the old age threaten their nutritional status. The Global Leadership Initiative on Malnutrition (GLIM) released new universal criteria for diagnosing and grading malnutrition, but the validation of these criteria in elderly cancer population is not well documented. Our objective was to investigate the application of the GLIM criteria in nutrition assessment and survival prediction in elderly cancer patients.

Methods: This retrospective cohort analysis was conducted on a primary cohort of 1192 cancer patients aged 65 years or older enrolled from a multi-institutional registry, and a validation cohort of 300 elderly cancer patients treated at the First Affiliated Hospital of Sun Yat-sen University. Patients considered at-risk for malnutrition based on the NRS-2002 were assessed using the GLIM criteria. The association between the nutritional status and patients' overall survival (OS) was then analyzed by the Kaplan–Meier method and a Cox model. A nomogram was also established that included additional independent clinical prognostic variables. To determine the predictive accuracy and discriminatory capacity of the nomogram, the C-index, receiver operating characteristic (ROC) curve and calibration curve were evaluated.

Results: The percentage of patients considered “at-risk” for malnutrition was 64.8% and 67.3% for the primary and validation cohorts, respectively. GLIM-defined malnutrition was diagnosed in 48.4% of patients in the primary cohort and 46.0% in the validation cohort. In the primary cohort, patients at risk of malnutrition (NRS-2002 ≥ 3) showed a worse OS than those with a NRS-2002 < 3 (HR 1.34, 1.10–1.64; $p = 0.003$). Additionally, patients with GLIM-defined severe malnutrition (HR1.71, 1.37–2.14; $p < 0.001$) or moderate malnutrition (HR1.35, 1.09–1.66; $p = 0.006$) showed a significantly shorter OS compared to those without malnutrition. The nomogram incorporating the domains of the GLIM with other variables was accurate, especially for predicting the 1- and 2-year overall survival rates.

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Conclusions: The GLIM criteria can be used in elderly cancer patients not only to assess malnutrition, but also to predict survival outcome. The nomogram developed based on the GLIM domains can provide a more accurate prediction of the prognosis than existing systems.

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1. Introduction

An aging population, coupled with healthcare advances, has led to an increase in the number of people aged 65 years and older. The world's elderly population will increase from 841 million in 2013 to 2 billion by 2050, comprising 21.1% of the entire population [1]. Although malignant diseases occur at all ages, more than half of all newly-diagnosed cancer patients, and 71% of cancer deaths, are in subjects 65 years old and older [2,3]. Because of the rapidly growing elderly population and the steady increase in cancer incidence with advancing age, there is expected to be a huge population of elderly cancer patients within the next few decades. This population is at particularly high risk for malnutrition due not only to aging, but also the disease itself, as well as the adverse effects of anti-cancer treatments. Specialized nutrition assessments and treatments are required for these patients because they have unique features that are different from younger patients.

Malnutrition in elderly cancer patients may lead to increased mortality and morbidity, extended hospital stays, a poorer quality of life, as well as reduced tolerance of oncologic therapy and increased therapy-related toxicities [4,5]. Early detection of malnutrition and subsequent nutritional intervention can significantly benefit elderly populations, and can also reduce medical/healthcare costs [6,7]. In order to standardize the diagnosis of malnutrition, the Global Leadership Initiative on Malnutrition (GLIM) recently developed and reported new universal criteria for diagnosing malnutrition in adults, based on a two-step model for risk screening and diagnostic assessment [8].

For patients considered to be at risk of malnutrition according to nutritional screening, the GLIM criteria recommend performing a nutritional assessment that includes phenotypic information (unintentional weight loss, low body mass index [BMI], and reduced muscle mass), as well as etiologic criteria (reduced food intake/assimilation and disease burden), using their provided optimal reference values and conditions. To diagnose malnutrition, at least one phenotypic criterion and one etiologic criterion should be present. In addition, the GLIM criteria also grade the severity of malnutrition as stage 1/moderate malnutrition or stage 2/severe malnutrition. Because the GLIM consensus criteria have only recently been proposed, it is important to validate them in various populations, including elderly cancer patients, and to determine their capacity to predict adverse clinical outcomes. Therefore, the purpose of this study was to examine the application of the GLIM criteria in elderly cancer patients.

2. Patients and methods

2.1. Study population

This retrospective analysis was conducted on a primary cohort of elderly cancer patients from a multicenter observational cohort study (Registration number: ChiCTR1800020329) including Daping Hospital of the Third Military Medical University, Fujian Cancer Hospital and the First Hospital of Jilin University between April 2013 and December 2018. The inclusion criteria were age 65 years or older and a diagnosis of a solid tumor at any stage. Variables where >10% of values were missing, or patients with a missing value for a specific variable, were excluded from the analysis. In

addition, an independent cohort of cancer patients with the same inclusion and exclusion criteria were enrolled from the First Affiliated Hospital of Sun Yat-sen University from October 2012 to July 2015, and this group of patients was used to form the validation cohort of this study. Ethical approval was obtained from the participating institutions through their respective institutional review boards.

2.2. Data collection

Demographic and clinicopathological data were collected, including sex, primary tumor site, TNM stage, Karnofsky Performance Status (KPS), alcohol consumption, smoking status, food intake or assimilation (digestion), hemoglobin and albumin. The T and N categories were not included in this analysis since each tumor type has distinct T/N categories. As there were insufficient data on the C-reactive protein level, other markers of the systemic inflammatory response, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), were included in the study. The metastasis (M) category was used instead of advanced tumor staging in the final Cox model. The KPS data were converted to the Eastern Cooperative Oncology Group Performance Status (ECOG PS) using the following categories [9]: KPS 100 (ECOG PS 0), KPS 90 to 80 (ECOG PS 1), KPS 70 to 60 (ECOG PS 2), KPS 50 to 40 (ECOG PS 3), and KPS 30 to 0 (ECOG PS 4). All pathological staging was defined according to the 8th edition of the AJCC TNM staging system. Albumin and hemoglobin were used as continuous variables, and widely accepted values were used to group patients. The optimal cut-off values for the NLR and PLR were generated according to the Youden index by a receiver operating characteristic (ROC) curve.

2.3. Nutritional assessment

All patients were initially screened using the Nutritional Risk Screening-2002 (NRS-2002), and a score of 3 or greater was considered the patient was at risk of malnutrition [8]. Subsequent assessment using the GLIM criteria was then conducted for the diagnosis and severity grading of malnutrition. The GLIM criteria are composed of three phenotypic criteria and two etiologic criteria. A combination of at least one phenotypic criterion and one etiologic criterion is necessary to make a diagnosis of malnutrition [8]. As cancer is an etiologic component of the GLIM criteria, patients who met any phenotypic criterion were diagnosed with malnutrition in this study.

Patients were asked to recall their weight within the past 6 months to estimate body weight changes. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). Although the GLIM criteria suggest that a reduced muscle mass should be diagnosed based on a body composition analysis (e.g., via bioelectrical impedance analysis, computed tomography or dual energy X-ray absorptiometry, etc), standard anthropometric measurements (like the calf circumference) are also acceptable in the clinical setting to assess reduced muscle mass. Therefore, the calf circumference [cm] of the right leg in the supine position with 90 degrees of knee flexion was used to quantify the muscle mass in our patients [8]. The following cut-offs were used to classify a reduced muscle mass: ≤ 30 cm in

men and ≤ 29 cm in women [10]. Reduced food intake was evaluated based on symptoms described by the patient, including decreased dietary intake or the presence of symptoms that impact food intake. Only phenotypic criteria are used in grading the severity according to the GLIM criteria [8]. To diagnose Stage 2/severe malnutrition, one of the following conditions had to be present: (i) weight loss $>10\%$ of the body weight within the past 6 months; (ii) low BMI, based on the optimal cut-off values in Asians described by Maeda et al. [11], (40–69 years old with BMI < 17.0 kg/m², ≥ 70 years with BMI < 17.8 kg/m²) or (iii) a severe deficit in muscle mass (calf circumference <27 cm in men and <26 cm in women). We also developed a nomogram incorporating the GLIM domains and additional clinical prognostic variables for better survival prediction.

2.4. Statistical analysis

Categorical variables were reported as whole numbers and proportions, and continuous variables were reported as medians with interquartile ranges (IQRs). The overall survival (OS) was defined as the length of time from the date of diagnosis to the date of death or date of last follow-up for censored patients. The overall survival was calculated using the Kaplan–Meier method and the log-rank test, and hazard ratios (HRs) were calculated using a univariate Cox regression analysis. A multivariate Cox regression analysis was also performed using backward selection to test the independent significance of different factors, including clinical variables and various GLIM criteria. On the basis of the results of the multivariable analysis, we formulated a nomogram using selected variables to predict the 1-, 2- and 3-year OS rates for elderly cancer patients at risk of malnutrition using the rms package in R. Harrell's C-index, calculated via a bootstrap method with 1000 resamples, was used to evaluate the discrimination performance of the nomogram. The area under ROC curve (AUC) was used to evaluate the predictive accuracy for the 1-, 2- and 3-year OS. Calibration curves were assessed graphically by plotting the observed rates against the nomogram-predicted probabilities. In all analyses, p values < 0.05 were considered to indicate statistical significance. All analyses were performed using the R software, version 3.6.1.

3. Results

3.1. Clinicopathological characteristics

In the primary cohort, there were initially 1281 patients. After the patients without a nutritional assessment ($n = 52$) and those patients who had missing values for any of the examined variables ($n = 37$) were excluded, a total of 1192 patients who met the inclusion criteria were finally enrolled in the study. For the validation cohort, we studied 300 consecutive patients admitted to a single institution. The demographic features and clinical characteristics of the primary and validation cohorts are presented in Table 1.

3.2. GLIM-defined malnutrition

A total of 772 (64.8%) patients in the primary cohort and 202 (67.3%) patients in the validation cohort were considered to be “at-risk” for malnutrition based on NRS-2002. According to the GLIM criteria, 577 (48.4%) patients in the primary cohort and 138 (46.0%) patients in the validation cohort were malnourished. The proportions of patients with moderate and severe malnutrition were found to be similar in both cohorts (27.8% in stage 1 and 20.6% in stage 2 in the primary group; 25.0% in stage 1 and 21.0% in stage 2 in the validation group). Table 2 shows the numbers of patients with each phenotypic criterion regarding GLIM-defined malnutrition.

Weight loss was the most common phenotypic factor that led to a diagnosis of malnutrition in both the primary and validation cohorts.

3.3. Association of malnutrition with overall survival

The median follow-up time was 15.6 months (IQR 9.3–27.9) for patients in the primary cohort. The patients with a high NRS-2002 score (≥ 3) had a worse OS than those with a lower NRS-2002 score (< 3) (HR 1.34, 1.10–1.64; $p = 0.003$) (Fig. 1). Based on the GLIM criteria, 577 patients were categorized as malnourished (331 patients in stage 1 and 246 patients in stage 2) and 615 patients were not malnourished. Both moderate (HR 1.35, 1.09–1.66; $p = 0.006$) and severe (HR 1.71, 1.37–2.14; $p < 0.001$) malnutrition were associated with a lower OS compared with patients who were not malnourished. Furthermore, patients with severe malnutrition showed a trend towards a shorter OS than those with moderate malnutrition (HR 1.27, 1.00–1.61; $p = 0.052$) (Fig. 2). After multivariable adjustment by clinical variables and several serum markers, severe malnutrition remained an independent prognostic factor for OS in elderly cancer patients in the primary cohort (Table 3). When stratified by tumor type, severe malnutrition was still associated with worse OS in patients with respiratory system tumors, digestive system tumors and other tumors (Fig. S1). Multivariate Cox regression analysis indicated that severe malnutrition was an independent prognostic factor of OS for patients with digestive system tumors, but not for patients with respiratory system tumors (Table S1).

3.4. Prognostic nomogram based on the GLIM domains and clinical variables

In the primary cohort, the individual domains of the GLIM criteria were included in a univariable analysis of elderly cancer patients at risk of malnutrition (Table S2). Among the various parameters, a low BMI, reduced muscle mass and reduced food intake were significantly associated with poorer overall survival. Three domains of the GLIM criteria (low BMI, reduced muscle mass and reduced food intake) and four clinical variables (M category, albumin, NLR and ECOG performance status) were found to be independent prognostic factors for the OS (Fig. 3).

A nomogram based on these seven factors was developed to predict the OS in elderly cancer patients at risk of malnutrition (Fig. 4). The scales of the nomogram reflect coefficients from the Cox model rescaled to a user-friendly 100-point range. The C-index for OS prediction was 0.71 (95% CI, 0.68 to 0.74). Furthermore, the model yielded AUC values of 0.77, 0.73 and 0.66 for predicting mortality at 1, 2 and 3 years after admission (Fig. 5). The calibration plot for the probability of survival at 1 and 2 years showed optimal agreement between the prediction by nomogram and the actual observed survival (Fig. 6). The accuracy of the nomogram was compared with the classic AJCC-TNM staging system in the primary cohort. The C-index for OS prediction was 0.60 by the AJCC-TNM staging system, which was significantly lower than the C-index by the nomogram (0.71; $p < 0.001$). In addition, the AUCs of the nomogram for predicting the 1-, 2- and 3-year overall survival rates exhibited superior survival predictive ability than that of the AJCC-TNM staging system (Fig. S2).

3.5. Validation of the predictive accuracy of the nomogram

In the validation cohort, the median follow-up time was 22.4 months (IQR 15.3–31.4). The nomogram had a C-index of 0.77 (95% CI, 0.72 to 0.81) for predicting the OS in elderly cancer patients at risk of malnutrition, and the overall survival rates were accurately

Table 1
Demographic and clinical characteristics of the elderly patients with cancer.

Demographic or clinical characteristic	Primary cohort (n = 1192), No. (%)		Validation cohort (n = 300), No. (%)	
	No risk of malnutrition (n = 420)	At risk of malnutrition (n = 772)	No risk of malnutrition (n = 98)	At risk of malnutrition (n = 202)
Sex				
Male	281 (66.9)	534 (69.2)	52 (53.1)	132 (65.3)
Female	139 (33.1)	238 (30.8)	46 (46.9)	70 (34.7)
Primary tumor site				
Digestive system	171 (40.7)	508 (65.8)	73 (74.5)	166 (82.2)
Respiratory system	143 (34.1)	160 (20.7)	4 (4.1)	5 (2.5)
Urogenital system	37 (8.8)	35 (4.6)	12 (12.2)	10 (4.9)
Others	69 (16.4)	69 (8.9)	9 (9.2)	21 (10.4)
TNM stage				
I	41 (9.8)	59 (7.7)	13 (13.3)	18 (8.9)
II	104 (24.8)	173 (22.4)	28 (28.6)	48 (23.8)
III	140 (33.3)	271 (35.1)	28 (28.5)	65 (32.2)
IV	135 (32.1)	269 (34.8)	29 (29.6)	71 (35.1)
M category				
M0	285 (67.9)	511 (66.2)	69 (70.4)	135 (66.8)
M1	135 (32.1)	261 (33.8)	29 (29.6)	67 (33.2)
ECOG performance status				
≤1	390 (92.9)	515 (66.7)	83 (84.6)	138 (68.3)
>1	30 (7.1)	257 (33.3)	15 (15.4)	64 (31.7)
Alcohol consumption				
Absent	339 (80.7)	605 (78.4)	88 (89.8)	166 (82.2)
Present	81 (19.3)	167 (21.6)	10 (10.2)	36 (17.8)
Smoking				
Absent	221 (52.6)	386 (50.0)	56 (57.1)	116 (57.4)
Present	199 (47.4)	386 (50.0)	42 (42.9)	86 (42.6)
Serum albumin, g/L				
Normal (>35)	321 (76.4)	400 (51.8)	71 (72.4)	121 (59.9)
Abnormal (≤35)	99 (23.6)	372 (48.2)	27 (27.6)	81 (40.1)
NLR				
High (≥3.5)	98 (23.3)	400 (51.8)	16 (16.3)	92 (45.5)
Low (<3.5)	322 (76.7)	372 (48.2)	82 (83.7)	110 (55.5)
PLR				
High (≥133)	225 (53.6)	484 (62.7)	52 (53.1)	110 (54.5)
Low (<133)	195 (46.4)	288 (37.3)	46 (46.9)	92 (45.5)
Hemoglobin, g/dL				
Normal (≥12)	270 (64.3)	380 (49.2)	52 (53.1)	74 (36.6)
Abnormal (<12)	150 (35.7)	392 (50.8)	46 (46.9)	128 (63.4)
Reduced food intake				
Absent	284 (67.6)	183 (23.7)	47 (48.0)	96 (47.5)
Present	136 (32.4)	589 (76.3)	51 (52.0)	106 (52.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; M, metastasis.

predicted by the nomogram with AUC values of 0.80, 0.72 and 0.78 for predicting mortality at 1, 2 and 3 years (Fig. 5). Furthermore, the calibration plots demonstrated that the predicted 1 and 2 years survival rates closely corresponded to the actual survival rates (Fig. 6).

4. Discussion

Malnutrition is common in older cancer patients [12], and is a major public health issue worldwide. The ESPEN guidelines recommend that a nutritional assessment should be performed for all patients with cancer at the time of diagnosis, but the prevalence of malnutrition varies based on the screening and assessment tools used [13,14]. In September 2018, the GLIM criteria were proposed in order to build a global consensus on the diagnostic criteria for malnutrition. Although the criteria were based on the collective experience of numerous experts, it is important to validate their relevance for clinical practice in a variety of patient sub-groups, including elderly cancer patients. In this multicenter, retrospective study, we verified the performance of the GLIM criteria in elderly cancer patients using 1192 patients as a primary cohort and

Table 2
The numbers of malnourished patients meeting each of the GLIM phenotypic criteria.

Nutritional characteristic	Phenotypic criteria			Malnutrition n (%)
	Low BMI, n (%)	Reduced muscle mass, n (%)	Weight loss, n (%)	
Primary cohort				
All	305 (25.6%)	289 (24.2%)	375 (31.5%)	577 (48.4%)
Stage 1/moderate	172 (14.4%)	219 (18.4%)	264 (22.1%)	331 (27.8%)
Stage 2/severe	133 (11.2%)	70 (5.8%)	111 (9.4%)	246 (20.6%)
Validation cohort				
All	69 (23.0%)	84 (28.0%)	98 (32.7%)	138 (46.0%)
Stage 1/moderate	39 (13.0%)	66 (22.0%)	66 (22.0%)	75 (25.0%)
Stage 2/severe	30 (10.0%)	18 (6.0%)	32 (10.7%)	63 (21.0%)

Abbreviations: BMI: body mass index.

300 patients as a validation cohort. The prevalence of malnutrition was 48.4%, with 27.8% of patients classified as having moderate malnutrition and 20.6% as having severe malnutrition in the primary cohort. Similarly, among the validation population, 25.0% of patients were moderately malnourished, and 21.0% were severely malnourished. We believe this is the first large-scale study of the prevalence of malnutrition in elderly cancer patients with solid tumors based on the GLIM criteria. Yilmaz et al. reported a lower incidence of malnutrition (34.5%) in elderly patients with hematological malignancies, but only 29 older participants were included in that analysis [15]. In a study conducted by Maeda et al. [11], GLIM-defined malnutrition was found to be present in 25.7% of elderly Asian patients (≥70 years), but the majority of those patients had non-cancer diseases, and it is expected that patients with cancer might have a higher risk of malnutrition compared with those with cardiac, respiratory and renal issues. There have been previous studies on the prevalence of malnutrition in elderly cancer patients based on other criteria. For example, in the post-hoc analysis of the NutriCancer 2012 study [16], the prevalence of malnutrition was found to be 44.9% in elderly cancer patients based on a standardized definition of malnutrition, which was similar to the rate in our present study. The prevalence of malnutrition in elderly cancer patients was reported to range from 27% to 46% in different studies using different criteria [16–18].

The relationship between malnutrition and survival has been described in previous studies [19–21], but the clinical relevance of GLIM-defined malnutrition to the survival of elderly cancer patients was unclear. The GLIM criteria categorizes patients into three groups: without malnutrition, moderate malnutrition (Stage 1) and severe malnutrition (Stage 2). This study showed that malnutrition (both moderate and severe) is associated with a shorter OS compared to patients without malnutrition. In addition, a non-significant trend toward a worse OS was observed in severely-malnourished patients compared to the moderately-malnourished patients in the primary cohort. Thus, GLIM-defined malnutrition was demonstrated to have good discriminatory ability for predicting the OS in elderly cancer patients. Our findings are in line with previous observations. For example, GLIM-defined malnutrition was reported to be a predictor of the 1-year mortality in patients with hematological malignancies [15]. In addition, Maeda et al. [11] found that patients with GLIM-defined malnutrition had significantly higher in-hospital mortality compared to those without malnutrition. The present study also found that GLIM-defined severe malnutrition had an independent negative effect on the OS in elderly cancer patients after adjusting for important confounders such as the M category and ECOG performance status. Similarly, the ESPEN diagnostic criteria for

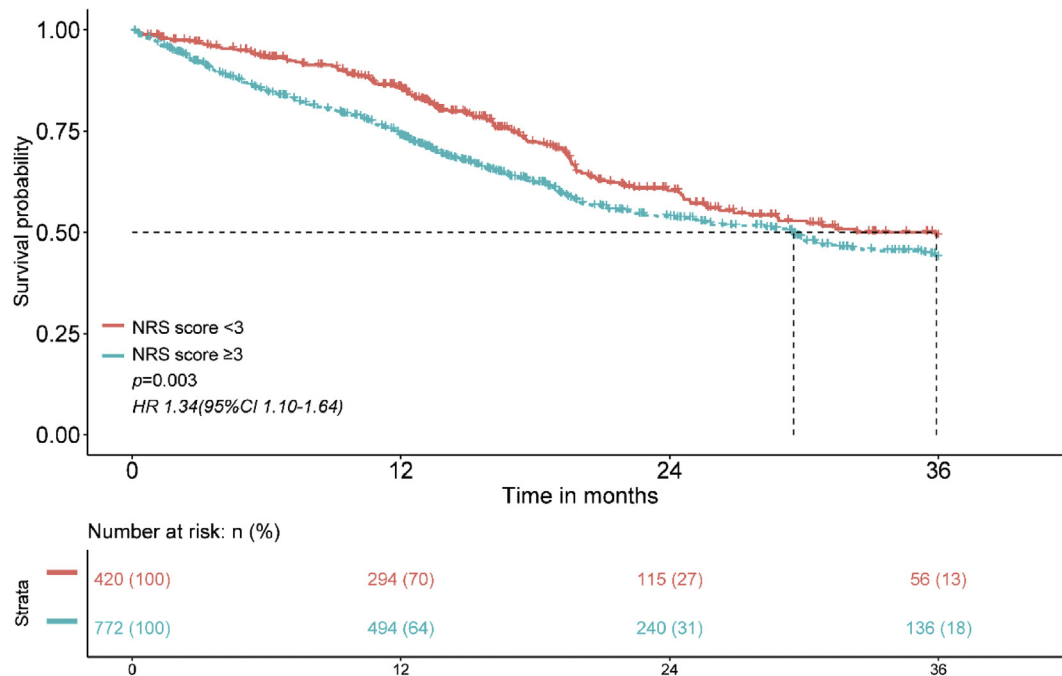


Fig. 1. Results of the Kaplan–Meier survival analysis for elderly cancer patients stratified by the NRS-2002 in the primary cohort.

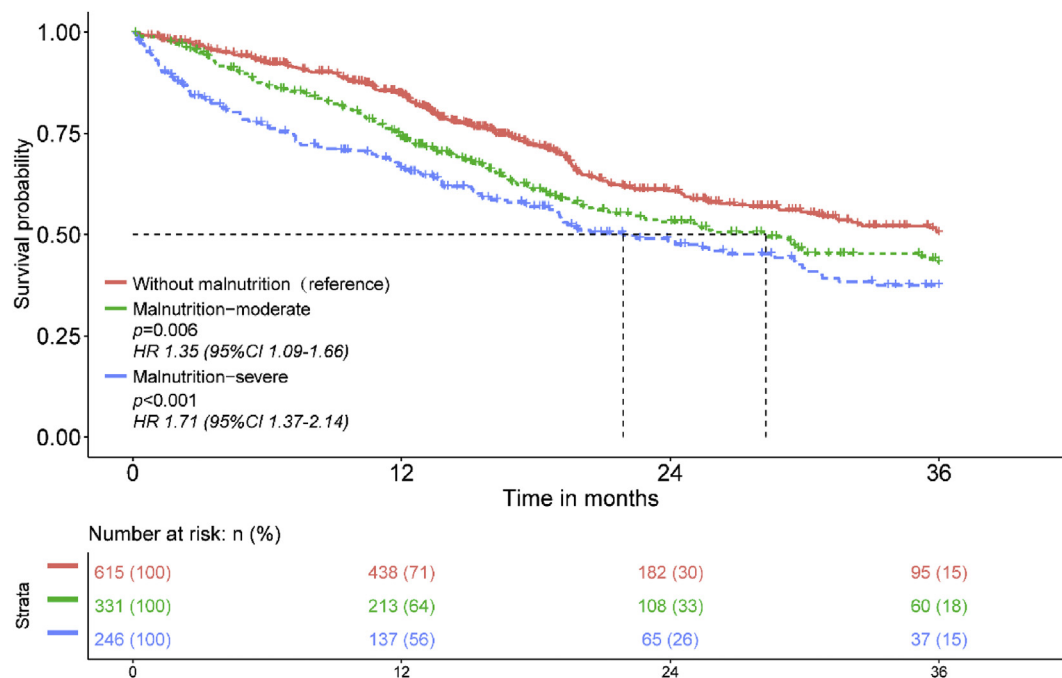


Fig. 2. Results of the Kaplan–Meier survival analysis for elderly cancer patients stratified by GLIM-defined malnutrition in the primary cohort. Overall survival stratified by “without malnutrition”, “moderate malnutrition” and “severe malnutrition”.

malnutrition were also reported to be a reliable predictor of the 3-year all-cause mortality among elderly inpatients [22]. Moreover, severe malnutrition was shown to be an independent prognostic factor in the setting of digestive system tumors, while it was not a significant prognostic factor for patients with respiratory system tumors. This study might provide preliminary evidence of the effectiveness of GLIM-defined malnutrition in elderly patients with digestive system tumors. However, future studies are still

recommended to investigate the prognostic impact of malnutrition on respiratory system tumors, because limited number of malnourished patients were included for the OS calculation in this subgroup.

GLIM-defined malnutrition has also been observed as a risk factor for other clinical adverse outcomes. In a retrospective study from the Norwegian Registry for Gastrointestinal Surgery (NoR-Gast), Skeie E et al. found that severe malnutrition was associated with increased risk of developing severe surgical complications and

Table 3

The results of the univariate and multivariate Cox regression analysis of the primary cohort of elderly cancer patients.

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Sex						
Male	Reference			Reference		
Female	0.83	0.68–1.01	0.058	0.86	0.68–1.09	0.207
Primary tumor site						
Digestive system	Reference			Reference		
Respiratory system	1.25	1.00–1.55	0.048	1.25	0.98–1.58	0.067
Urogenital system	1.11	0.78–1.59	0.552	1.38	0.95–2.00	0.089
Others	0.92	0.69–1.24	0.595	1.17	0.86–1.59	0.315
TNM stage						
I	Reference					
II	0.98	0.66–1.46	0.931			
III	1.28	0.89–1.86	0.188			
IV	2.25	1.56–3.24	<0.001			
M category						
M0	Reference			Reference		
M1	2.06	1.71–2.48	<0.001	1.94	1.60–2.36	<0.001
ECOG performance status						
≤1	Reference			Reference		
>1	2.10	1.74–2.54	<0.001	1.73	1.40–2.14	<0.001
Reduced food intake						
Absent	Reference			Reference		
Present	1.52	1.25–1.84	<0.001	1.26	1.03–1.56	0.026
GLIM-defined malnutrition						
Without malnutrition	Reference			Reference		
Moderate	1.35	1.09–1.66	0.006	1.16	0.94–1.44	0.175
Severe	1.71	1.37–2.14	<0.001	1.42	1.12–1.79	0.004
Alcohol consumption						
Absent	Reference			Reference		
Present	1.22	0.99–1.52	0.065	1.17	0.92–1.49	0.189
Smoking						
Absent	Reference			Reference		
Present	1.19	0.99–1.43	0.053	0.98	0.78–1.23	0.873
Serum albumin, g/L						
Normal (>35)	Reference			Reference		
Abnormal (≤35)	1.54	1.29–1.85	<0.001	1.18	0.97–1.43	0.096
NLR						
Low (<3.5)	Reference			Reference		
High (≥3.5)	1.64	1.37–1.96	<0.001	1.28	1.05–1.55	0.013
PLR						
Low (<133)	Reference					
High (≥133)	0.87	0.73–1.05	0.139			
Hemoglobin, g/dL						
Normal (≥12)	Reference					
Abnormal (<12)	1.05	0.87–1.26	0.615			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GLIM, Global Leadership Initiative on Malnutrition; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; M, metastasis.

postoperative mortality [23]. In addition, GLIM-defined malnutrition was reported to be negatively associated with European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) summary scores in patients with lung cancer [24]. Similarly, the current study suggested that malnourished patients showed a higher prevalence of poorer ECOG PS (ECOG PS > 1) than patients without malnutrition (34.5% vs. 14.3%; $p < 0.001$).

We established a nomogram model that included domains of the GLIM criteria to precisely predict the prognosis of elderly cancer patients at risk of malnutrition, and the nomogram was more accurate than the conventional AJCC TNM staging system. In the nomogram, the domains of the GLIM criteria (reduced muscle mass, low BMI and reduced food intake) were significantly associated with the prognosis of patients in a multivariate analysis. Inflammatory markers, including the NLR and albumin level, have previously been suggested to be independent risk factors for the prognosis of cancer patients, and thus further improved the nomogram [25,26]. In addition, tumor metastasis and an ECOG performance status >1 are strong risk factors [19,26]. The nomogram was able to predict an

individual's 1-, 2- and 3-year survival rates with good accuracy, with especially high value for the 1- and 2-year overall survival rates, and its performance was verified in the validation cohort. Moreover, all factors included in the nomogram are commonly assessed in routine clinical practice, in both hospitalized and ambulatory patients, which is clearly a practical advantage.

Some limitations of this study should be discussed when considering the results. First, since this study is a retrospective analysis of an observational cohort, the Short Form of the Mini Nutritional Assessment (MNA-SF), which is a commonly-employed screening device adapted for older adults, was not utilized for assessing patients at risk of malnutrition. Second, the optimal thresholds for reduced muscle mass to classify the severity of malnutrition remain unknown, so we referenced the cut-off values for diagnosing sarcopenia from a study of hospitalized patients aged ≥65 years [10]. Optimal malnutrition-specific thresholds still need to be clarified in future studies. Third, the association between GLIM-defined malnutrition and other clinically-relevant outcome measures, i.e. mobility, physical functioning, quality of life, should also be studied in the future.

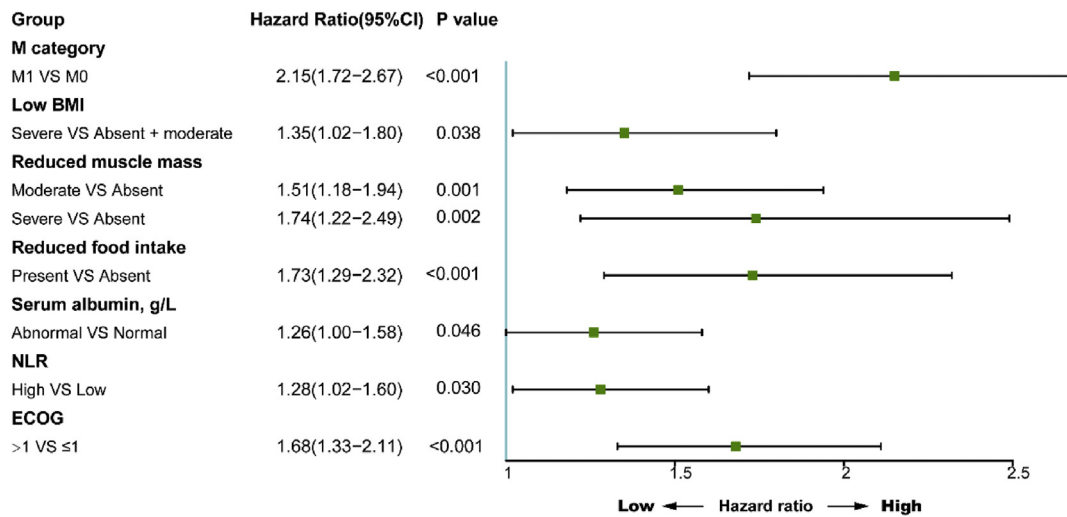


Fig. 3. Multivariate Cox regression analysis based on GLIM domains and clinical variables of the primary cohort of elderly cancer patients at risk of malnutrition. NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index.

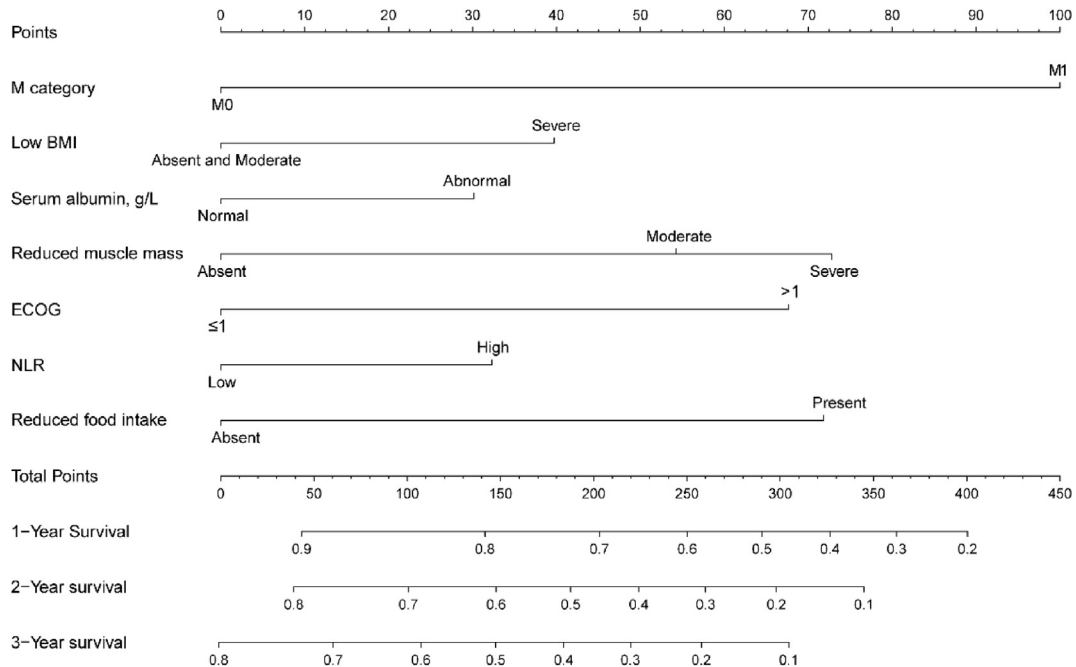


Fig. 4. The nomogram developed to predict the overall survival of elderly cancer patients at risk of malnutrition. (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable's value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the likelihood of survival at 1, 2 or 3 years). NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index.

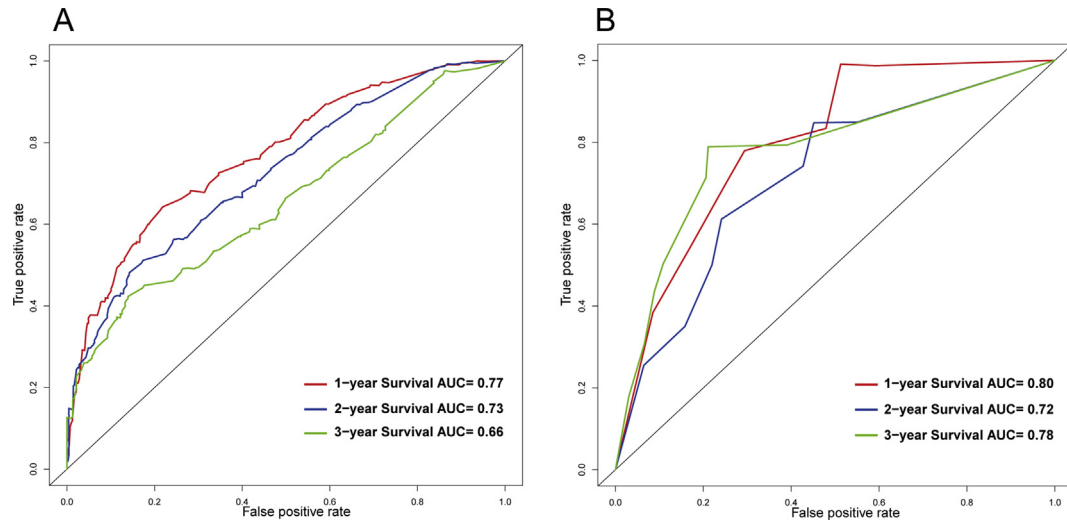


Fig. 5. Area under the ROC curves (AUC) for predicting the overall survival at 1, 2 or 3 years in the primary cohort (A) and the validation cohort (B). ROC: receiver operator characteristic.

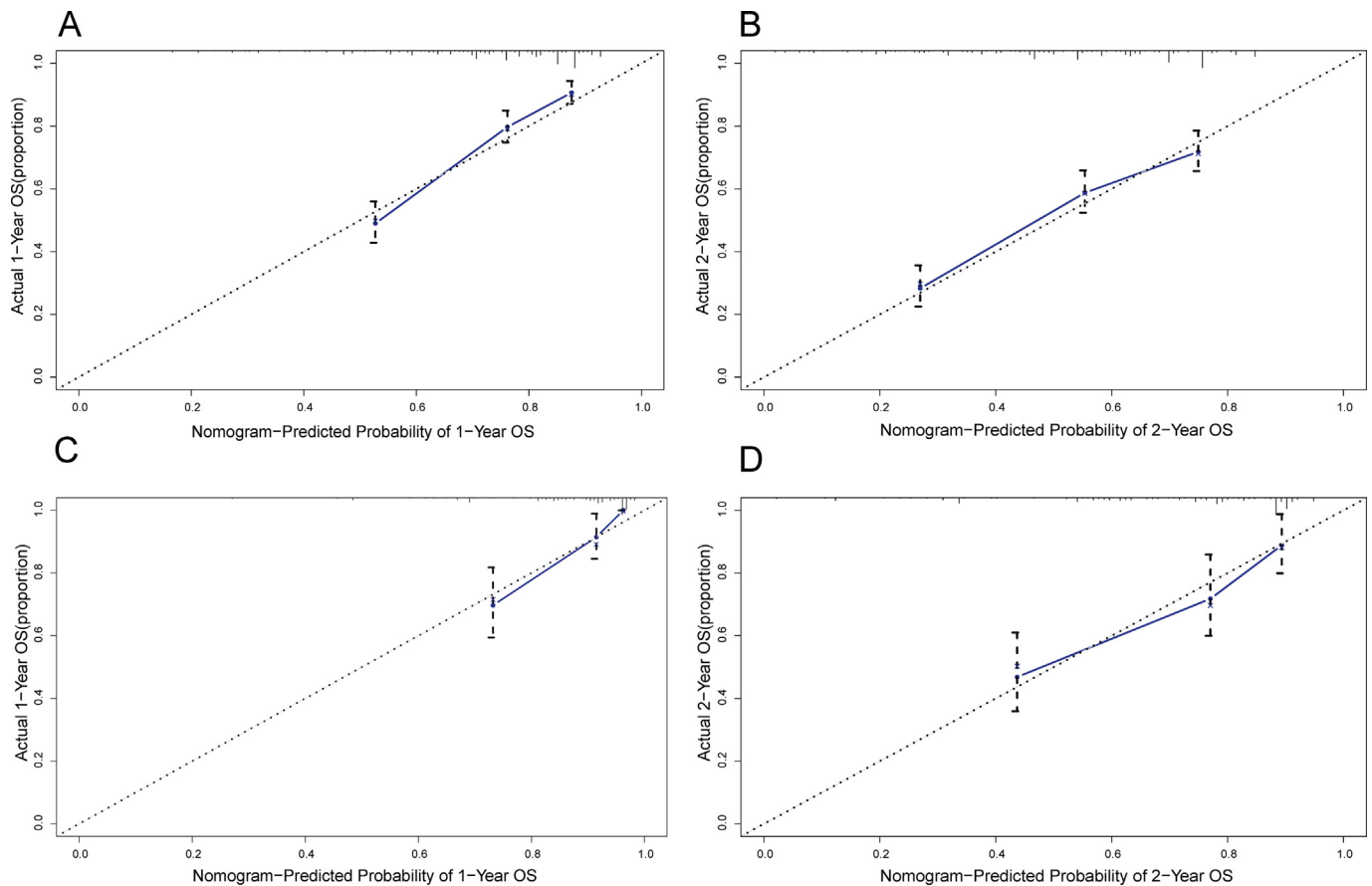


Fig. 6. The calibration curve for predicting patient survival at (A) 1 year and (B) 2 years in the primary cohort and at (C) 1 year and (D) 2 years in the validation cohort. The nomogram-predicted probability of overall survival is plotted on the x-axis; the actual overall survival is plotted on the y-axis. OS: overall survival.

5. Conclusion

In this study, we found that the GLIM criteria could not only diagnose malnutrition, but could also predict the overall survival of elderly cancer patients. A nomogram including GLIM domains may enhance the predictive accuracy for the survival of elderly cancer patients.

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Data and materials availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the [Supplementary Materials](#). Additional data related to this paper may be requested from the authors.

Author contributions

HPS conceived and designed the study. MT, RB and TC assisted with the development of the methods. XZ and QZ did the data analysis. XZ and KPZ drafted the initial manuscript. All authors assisted with the interpretation of the findings, commented on drafts of the manuscript, and approved the final version. HPS is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflicts of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2020.08.004>.

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