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Original article

Scored-GLIM as an effective tool to assess nutrition status and predict survival in patients with cancer

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SUMMARY

Background & aims: The Global Leadership Initiative on Malnutrition (GLIM) released new universal criteria for diagnosing and grading malnutrition, and calls for further investigations not only in different clinical setting but also in GLIM itself including reference value, combination and weight of different GLIM criteria. This study aimed to weigh the GLIM criteria and develop a scored-GLIM system, and then validate as well as evaluate its application in nutritional assessment and survival prediction for patients with cancer.

Design: A total of 3547 patients in the primary cohort and 415 patients in the validation cohort were included in the study. Patients' nutritional status were retrospectively assessed using the GLIM criteria. Kaplan–Meier survival curves and multivariate Cox regression analyses were performed to analyze the association between nutritional status and overall survival (OS). A nomogram was produced to quantify the GLIM criteria and develop the scored-GLIM system. C-index, receiver operating characteristic (ROC) curve and calibration curve analyses were performed to validate the predictive accuracy and discriminatory capacity of the scored-GLIM. Finally, a decision curve was applied to assess the clinical utility of the scored-GLIM system.

Results: In the primary cohort, 70.3% of patients were diagnosed as malnutrition. The malnutrition severity grading according to the GLIM criteria were associated with the prognosis of patients with cancer (HR 1.42, 1.23 to 1.65 for moderate malnutrition; HR 1.80,1.84 to 2.09 for severe malnutrition). The weight of each GLIM criteria was calcu-

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lated, and unintentional weight loss was the most determining factor acting upon mortality (HR 1.82, 1.64 to 2.10 for stage II and HR 1.50, 1.31 to 1.73 for stage I). A nomogram was constructed by four factors of GLIM to weigh the GLIM criteria. The areas under the ROC curve were 65.3 (1-year ROC) and 65.5 (3-year ROC), and the C-index was 0.62, and the calibration curves fitted well. Decision curve analysis demonstrated the clinical usefulness of the scored-GLIM system.

Conclusion: The accuracy and net clinical benefit of scored-GLIM system were similar to scored-PG-SGA but higher than GLIM both in nutrition assessment and in survival prediction for patients with cancer. These findings, along with its time-savings advantages over scored-PG-SGA, suggest scored-GLIM be a better nutritional assessment tool.

1. Introduction

Cancer-related malnutrition is a common diagnosis in patients with cancer, with determinants linked to the patients' individual habits, the tumor itself, and the treatments. Although malnutrition is a global concern associated with increased morbidity, mortality, and cost, there has been a lack of consensus on diagnostic criteria in clinical settings. None of existing approach were globally accepted, and different studies utilized different assessment tools to diagnose malnutrition [1]. It is also important to note that many of the existing nutrition screening and assessment approaches have not been rigorously validated [2].

Because of its well-known prognostic value, the diagnostic criteria of malnutrition have received a lot of attention in recent years, especially among patients with cancer, a population at high risk of malnutrition [3]. Both basic research and clinical care over the past decades had urgently needed a globally accepted diagnostic criteria for malnutrition. In response, the Global Leadership Initiative on Malnutrition (GLIM) has been launched [4].The GLIM approach consists of two steps, namely nutritional risk screening using any validated method, and malnutrition diagnosis, which requires that patients to meet at least one phenotypic criterion (unintentional weight loss, low body mass index, or reduced muscle mass) and one etiologic criterion (reduced food intake or nutritional assimilation, severe disease/disease burden/inflammation). After the diagnosis of malnutrition, its severity could be graded by variations in any of the phenotypic criteria.

The PG-SGA has been widely used as a reference method for nutrition assessment in patients with cancer. The scored-PG-SGA, by providing a numerical scoring system, helps grading patients into severity triage. Compared with previous nutrition assessment tools such as SGA and PG-SGA, etc. GLIM has several advantages. It is time-saving and easy-to-implement. More importantly, it provides more alternative diagnostic choices for the first time. Two etiologic criteria with three phenotypic criteria will result six different diagnostic combinations. However, different diagnosis combination of the GLIM criteria might lead to discrepancy in nutrition diagnosis and survival prediction [5]. Therefore, the GLIM criteria and its different combination needs to be further weighted. To address this problem, we developed a scored-GLIM system and tested its accuracy in survival prediction for patients with cancer.

2. Materials and methods

2.1. Study population

This is a retrospective analysis of data collected from the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project of China (Registration number: ChiCTR1800020329). The INSCOC study is an observational, multi-centered, and hospital-based prospective cohort study and is conducted to investigate the prevalence of malnutrition in cancer patients and its relationship with overall survival, length of hospital stay and hospital costs [6–8]. Participants were followed from the initial admission until they died or until the end of December 2018. Patients who were diagnosed to be at risk of malnutrition by the NRS-2002 [9], were included in the study, and were excluded if they stayed at the hospital for less than 48 h. Also, as shown in the study schema (Fig. 1), patients who were missing the critical values such as the physical examination or follow-up data were excluded. Finally, 3547 patients were included in the present study.

All cases were consecutively enrolled between July 2013 and December 2018, and each patient was assessed for their nutritional status by a professionally trained dietitian. The anthropometric information, laboratory data, existing comorbidities, general information, nutrition related information and the medical history were collected for all patients within the first 48 h after admission. The cancer treatment related information and follow-up information were also documented. All pathological staging was defined according to the 8th edition of the AJCC TNM staging system. The main outcome of the study was the long-term mortality in the INSCOC-survival cohort during a 5-year follow-up. This study was approved by the medical ethical review committee of the registration hospital mentioned above and was carried out in accordance with the Declaration of Helsinki.

In addition, another group of consecutive cancer patients (n = 415) with the same inclusion and exclusion criteria were enrolled and followed up from October 2012 to July 2019, and this group of patients was used to form the validation cohort of this study.

2.2. Malnutrition according to GLIM criteria

The parameters used for the GLIM diagnosis and severity grading have been described previously [10]. Briefly, after identifying the patients at risk of malnutrition, the three phenotypic criteria and two etiologic criteria were used for the diagnosis and grading of the severity of malnutrition. At least one phenotypic and one etiologic criterion were required to diagnose malnutrition.

The following etiologic criteria were used based on data that were available: low food intake was defined based on the self-reported food intake prior to admission for one week or more, and any symptoms that might affect intake [10]. As all patients with cancer met the etiological components of the GLIM criteria, the disease burden/inflammation condition was not considered in this study. For the phenotypic criteria, unintentional weight loss was assessed by asking about the patients' body weight six month before and comparing that with

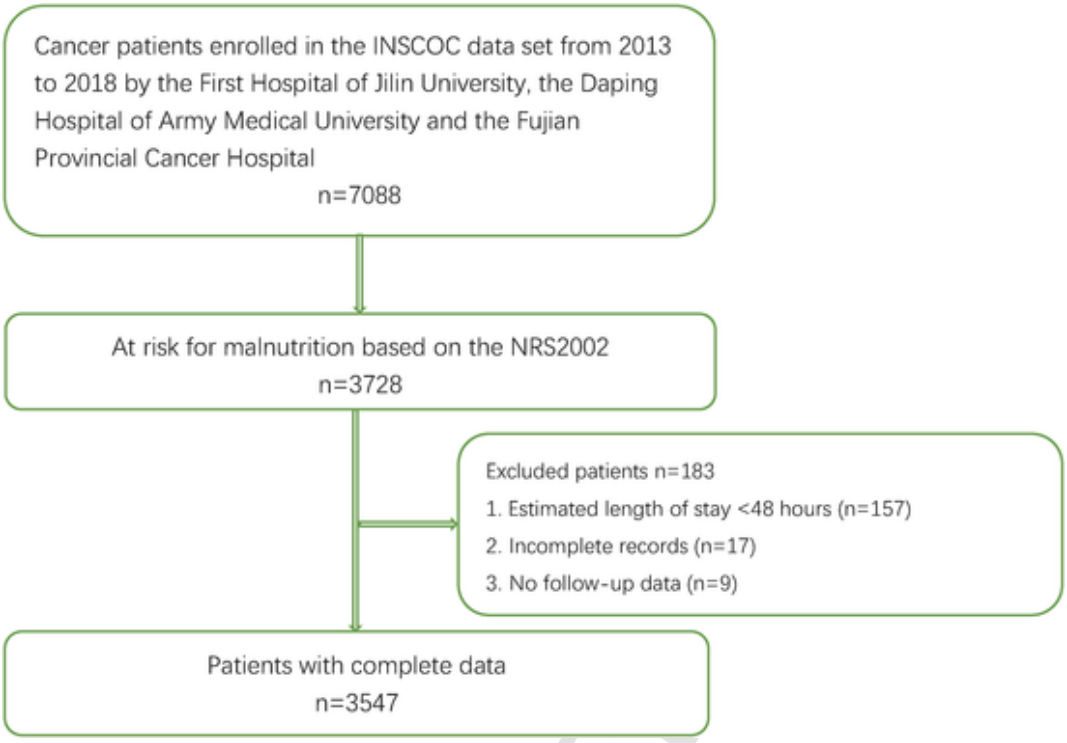

Fig. 1. A flow chart of the patient inclusion.

the weight measured in the hospital. The percentage of weight loss (unintentional) over 6 months was then calculated [11]. The body mass index (BMI; kg/m^2) was calculated from the weight, measured with a weighing scale adjusted to 0.1 kg, and height (Standing height (m)). Mid-arm circumference (MAC) and calf-circumference (CC) was measured using a flexible and non-elastic tape. The value of MAC was used to estimate arm muscular circumference (AMC). Hand grip strength (HGS) was measured in the dominant hand with a Jamar dynamometer. These values were used to estimate body weight standardized HGS (HGS/W, HGS divided by body weight).

The GLIM severity grading of malnutrition was defined as Stage I (moderate) and Stage II (severe) malnutrition using phenotypic grading as described previously [10]. Reduced muscle mass was evaluated via the AMC and CC for the quantity of muscle and the HGS/W was used as a supportive measure for function assessments [10,12]. A value lower than the fifth percentile (p5) or fifteenth percentile (P15) of for AMC, CC and HGS/W was considered separately by gender [13,14]. Unintentional weight loss >10% was another condition for identification of Stage II malnutrition. For low BMI, due to the lack of referenced BMI data for Asian populations for the evaluation of stage II (severe malnutrition), only stage I (moderate malnutrition, BMI<18.5) was diagnosed (Table 1).

2.3. Development and validation of a scored-GLIM for survival prediction

Three phenotypic criteria and one etiologic criterion were used as predictors. A multivariate cox regression analysis was applied to validate the association between the GLIM criteria and survival. Each criteria of GLIM were used to develop a nomogram based on its hazard ratio. First, according to the nomogram, the total points for each patient were calculated. Then, the optimal cut-off points for the points of scored GLIM were generated by using X-tiles software, according to the highest ×2 value defined by K-M survival analysis and log-

Table 1
Parameters and thresholds used for GLIM severity grading in the present study.

Grade	Phenotypical criteria		
	Weight loss (%)	Low BMI (kg/m^2)	Reduced muscle mass [a,b]
Stage I/Moderate malnutrition [a]	5–10% within the past 6 months, or 10–20% beyond 6 months	<18.5 if < 70 year, <20 if ≥ 70 year	Calf circumference < p15, weight standardized hand grip strength < p15, mamc < p15
Stage II/Severe malnutrition [a]	>10% within the past 6 months, or >20% beyond 6 months	Not applicable, no Asian standards	Calf circumference < p5, weight standardized hand grip strength < p5, mamc < p5

[a] Male and female are evaluated separately.
[b] Requires one phenotypic criterion meeting this grade; percentile values of calf circumference (male: p15 = 30.0 cm, p5 = 27.5 cm; female: p15 = 29 cm, p5 = 27 cm); percentile values of weight standardized hand grip strength (hand grip strength/weight, male: p15 = 0.3305, p5 = 0.2267; female: p15 = 0.2144, p5 = 0.1375), mamc (male:p15 = 18.66 cm, p5 = 16.49 cm; female: p15 = 17.06 cm, p5 = 15.08 cm).

rank test [15]. The nutritional status of the patients will be divided into four categories (normally nourished, mild malnutrition, moderate malnutrition, and severe malnutrition) based on the total points of each criteria of GLIM. The performance of scored GLIM and the discriminative ability were measured by calculating the Harrell's C-index (C-index, calculated via a bootstrap method with 1000 resamples) [16]. The area under ROC curve (AUC) was used to evaluate the predictive accuracy for the 1- and 3-year OS. Calibration of the nomogram for 1- and 3-year OS was performed by comparing the predicted survival with observed survival [17]. Spearman's analysis was used to test correlation between scored-GLIM and scored PG-SGA. Then, decision curve analysis (DCA) was performed to measure the clinical usefulness of the scored GLIM compared to scored PG-SGA and GLIM [18].

2.4. Statistical analysis

Quantitative variables expressed as mean ± standard and the difference were analyzed using Students t-test. For variables not following a normal distribution, non-parametric tests (Mann Whitney or Kruskall Wallis) was used. Comparison between qualitative variables was performed using a chi-square test, with Fisher correction if necessary. The Kaplan–Meier curve and Cox regression were used to analyze survival data. A multivariate cox regression analysis was also performed using backward selection to adjust for potential confounders. For calculations, significance was set at $p < 0.05$ for two tails. All analysis were performed using R (version 3.6.2, http://www.rproject.org/, rms package, survival package, survminer packages).Additionally, the decision curve analysis (DCA) was performed using the source file “stdca.r”, which was downloaded from https://www.mskcc.org/.

3. Results

3.1. Baseline characteristic of the study population

The demographic features and clinical characteristics of primary cohort and validation cohort were presented in Table 2. In the primary cohort, a total of 3547 patients with cancer were evaluated. The mean age was 59.1 ± 12.8 years, and 56.1% of the patients were male. Most patients (70.7%) were diagnosed with advanced cancer (31.1% stage III, 39.6% stage IV). The frequently diagnosed malignant neoplasms were colorectal cancer (26.6%), gastric cancer (19.1%), lung cancer (17.7%) and breast cancer (9.6%). The levels of AMC, HGS/W, CC, and albumin in malnourished patients were significantly reduced, while the 30-day mortality rate was increased. Furthermore, the most frequent nutrition impact symptoms were loss of appetite (20.8%), pain (13.4%), satiety (11.9%) and nausea (9.7%) (supplementary table 1).

3.2. The association of nutritional status with the patient prognosis

The patients’ nutritional status was retrospectively assessed with the GLIM criteria. 70.3% (n = 2495) of the patients were diagnosed with malnutrition, among whom, 41.3% were moderate (n = 1464) and 29.1% were severe (n = 1031). Kaplan–Meier curves were performed to show the association between the GLIM and survival. Patients in the malnutrition group had poorer OS compared to those in the normally nourished group (Fig. 2A). Moreover, severity of malnutrition was associated with OS (Fig. 2B). Cox models confirmed that an increasing risk of mortality was significantly associated with malnutrition by GLIM criteria. After multivariable adjustment by confounding variables, severe malnutrition remained an independent prognostic factor. The patients with severe (stage II) malnutrition had a 1.28 (95% CI, 1.04 to 1.59) elevated risk of death compared to those normally nourished (supplementary table 2).

3.3. The most important predictors of GLIM criteria for survival prediction

Whether the mortality risk trend of each indicator in the GLIM criteria was consistent? Multivariable analysis revealed that unintentional weight loss was the most determining factor acting upon mortality (HR 1.82, 95% CI: 1.64 to 2.10 for stage II and HR 1.50, 95% CI: 1.31 to 1.73 for stage I). The presence of a reduced BMI showed a much less pronounced effect on the increasing risk of death (HR 1.36,95% CI: 1.18 to 1.55 for stage I). Reduced muscle mass (HR 1.53, 95% CI: 1.17 to 1.96 for stage II and HR 1.21,95% CI: 1.11 to 1.43 for stage I) and reduced food intake or assimilation (HR 1.58,95% CI: 1.38 to 1.82) showed a moderate impact on survival (Table 3).

3.4. Development and validation of a nomograms to quantify the GLIM criteria

A nomogram was constructed by four factors of GLIM to quantify the GLIM criteria (Fig. 3A). Each subtype within these variables was assigned a score on the point scale. A Scored-GLIM to determine the estimated probability of survival at each time point was easily got by adding the total score and locating it on the total point scale. The C-index for OS prediction was 0.62 (95% CI: 0.61 to 0.64). Furthermore, the model yielded an AUC of 65.3 and 65.5 for prediction of mortality at 1-, and 3- year (Fig. 3D). The calibration curves revealed high agreement between predicted probabilities and actual observed survival in 1 and 3 years (Fig. 3B and C).

In the validation cohort, the nomogram had a C-index of 0.56 (95%CI: 0.52 to 0.63) for predicting OS in patients with cancer. The nomogram accurately predicted the overall survival probability, and the 1-year and 3-year AUC values were 63.8 and 56.6, respectively. Finally, the calibration curves showed that the predicted survival probabilities closely corresponded to the actual survival probabilities (supplementary Fig. 1).

3.5. Clinical application of the Scored-GLIM system

The accuracy of the scored-GLIM system was used to compare with the classic scored PG-SGA system and conventional GLIM system in the primary cohort. The c-index of scored-GLIM(0.62) was similar to that of the scored PG-SGA system (0.63), but was significantly higher than that of conventional GLIM(0.57). In addition, the AUCs of the nomogram for predicting the 1- and 3-year overall survival rates exhibited similar survival predictive ability with that of the scored PG-SGA system, but was significantly higher than that of the conventional GLIM system (Fig. 4A).

The correlation between scored-GLIM and scored PG-SGA was moderate between male ($r = 0.7$ $p < 0.001$) and female ($r = 0.72$ $p < 0.001$) (Fig. 4B). The optimal cutoffs of the scored-GLIM were 2.7–7 for mild malnutrition, 8.6–12.8 for moderate malnutrition, and 13.8–26.8 for severe malnutrition

Table 2
Detailed baseline characteristics of the study population.

Characteristics	GLIM diagnosis					
	Primary cohort by GLIM diagnosis n = 3547			Validation cohort by GLIM diagnosis n = 415		
	Normally nourished n = 1052	Malnutrition		Normally nourished n = 69	Malnutrition	
		Moderate n = 1464	Severe n = 1031		Moderate n = 195	Severe n = 151
General information						
30 days mortality, n, (%)	14 (1.3)	20 (1.3)	43 (4.1)	2 (2.8)	4 (2.0)	10 (6.6)
Age, years, mean (SD)	57.9 (11.5)	59.4 (12.7)	59.9 (12.8)	59.8 (10.8)	58.06 (13.7)	59.7 (13.8)
Sex, male, n (%)	509 (48.3)	851 (58.1)	629 (61.0)	45 (65.2)	118 (60.5)	73 (48.3)
Chronic disease history, n (%)						
0	634 (60.3)	938 (64.1)	641 (62.2)	49 (71.0)	159 (81.5)	108 (71.5)
1	268 (25.5)	364 (24.9)	269 (26.1)	15 (21.7)	30 (15.4)	38 (25.2)
2	105 (10.0)	117 (8.0)	85 (8.2)	3 (4.3)	5 (2.6)	2 (1.3)
3	45 (4.3)	45 (3.1)	36 (3.5)	2 (2.9)	1 (0.5)	3 (2.0)
Smoking, yes, n (%)	400 (38.0)	660 (45.1)	471 (45.7)	30 (43.5)	92 (47.2)	61 (40.4)
Drinking, yes, n (%)	212 (20.2)	308 (21.0)	211 (20.5)	17 (24.6)	41 (21.0)	27 (17.9)
PN, yes, n (%)	263 (25.0)	429 (29.3)	374 (36.3)	11 (15.9)	54 (27.7)	46 (30.5)
EN, yes, n (%)	321 (30.5)	515 (35.2)	393 (38.1)	16 (23.2)	59 (30.3)	55 (36.4)
Surgery, yes, n (%)	805 (76.5)	1053 (71.9)	724 (70.2)	38 (55.1)	53 (27.2)	47 (31.1)
Radiation, yes, n (%)	128 (12.2)	212 (14.5)	152 (14.7)	11 (15.9)	63 (32.3)	39 (25.8)
Chemotherapy, yes, n (%)	552 (52.5)	824 (56.3)	575 (55.8)	20 (29.0)	120 (61.5)	87 (57.6)
Stages, n (%)						
I	168 (16.0)	133 (9.1)	68 (6.6)	6 (8.7)	15 (7.7)	3 (2.0)
II	222 (21.1)	276 (18.9)	172 (16.7)	15 (21.7)	48 (24.6)	31 (20.5)
III	327 (31.1)	477 (32.6)	299 (29.0)	19 (27.5)	59 (30.3)	44 (29.1)
IV	335 (31.8)	578 (39.5)	492 (47.7)	29 (42.0)	73 (37.4)	73 (48.3)
Nutrition related information						
BMI, kg/m ^{2}, mean (SD)	23.7 (2.9)	21.2 (3.3)	20.1 (3.4)	23.0 (3.0)	19.3 (2.9)	18.4 (3.2)
AMC, cm, mean (SD)	22.1 (4.2)	20.5 (2.7)	18.8 (3.5)	23.9 (3.14)	21.54 (1.6)	17.8 (3.9)
HGS/W, (%)	44.1 (17.3)	43.6 (18.7)	38.3 (21.4)	54.1 (20.3)	47.4 (20.2)	37.6 (21.2)
CC, cm, mean (SD)	34.4 (2.7)	32.1 (3.0)	29.8 (4.3)	34.1 (2.5)	31.2 (2.8)	28.1 (5.0)
Albumin, g/L, mean (SD)	38.8 (7.21)	37.5 (13.85)	35.8 (11.9)	37.49 (5.14)	38.40 (6.55)	35.35 (5.7)
Neutrophils, 10 ^{9}/L, mean (SD)	4.8 (5.4)	5.3 (7.2)	5.8 (6.9)	4.6 (3.2)	4.7 (4.4)	5.6 (4.4)
Lymphocyte, 10 ^{9}/L, mean (SD)	1.8 (5.5)	1.5 (1.3)	1.7 (5.1)	1.90 (1.8)	1.61 (2.53)	1.3 (1.4)

BMI: body mass index, AMC: arm muscle circumference, HGS/W: body weight standardized hand grip, CC: calf-circumference, PN: parenteral nutrition, EN: enteral nutrition.
Chronic disease history 0–4 represent the number(s) of comorbid disease(s) reported by the patient (including chronic hepatitis or cirrhosis, diabetes, coronary heart disease, hypertension and others).

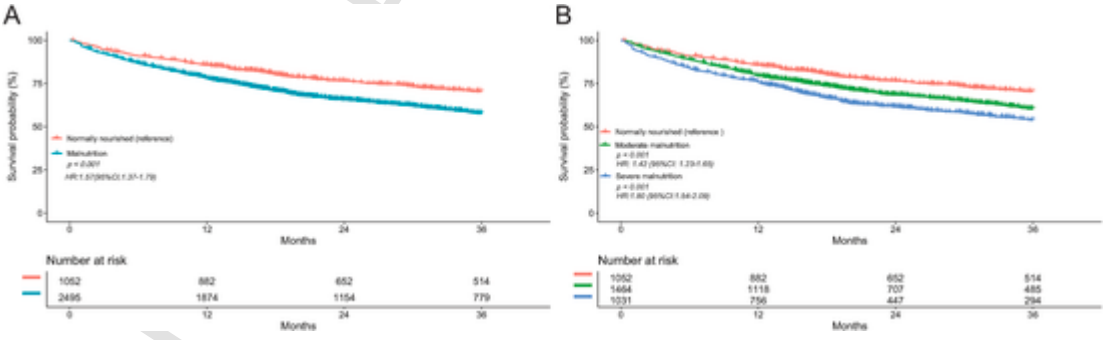

Fig. 2. Kaplan–Meier curve stratified by the GLIM criteria (A). Kaplan–Meier curve stratified by the GLIM severity grade (B).adjusted HR: adjusted by age, Chemotherapy, tumor stage, primary tumor site, Albumin, NLR. NLR: neutrophil-to lymphocyte ratio.

Table 3
The univariable and multivariable cox regression analysis of the each GLIM criteria.

GLIM criteria	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
unintentional weight loss						
Absent	Reference			Reference		
Stage I	1.54	1.35–1.75	<0.001	1.50	1.31–1.73	<0.001
Stage II	1.88	1.61–2.19	<0.001	1.82	1.64–2.10	<0.001
Reduce muscle						
Absent	Reference			Reference		
Stage I	1.30	1.16–1.46	<0.001	1.21	1.11–1.43	<0.001
Stage II	1.87	1.44–2.44	<0.001	1.53	1.17–1.96	<0.001
Low BMI						
Absent	Reference			Reference		
Stage I	1.56	1.38–1.76	<0.001	1.36	1.18–1.55	<0.001
Reduce intake						
Absent	Reference			Reference		
Present	1.63	1.43–1.86	<0.001	1.58	1.38–1.82	<0.001

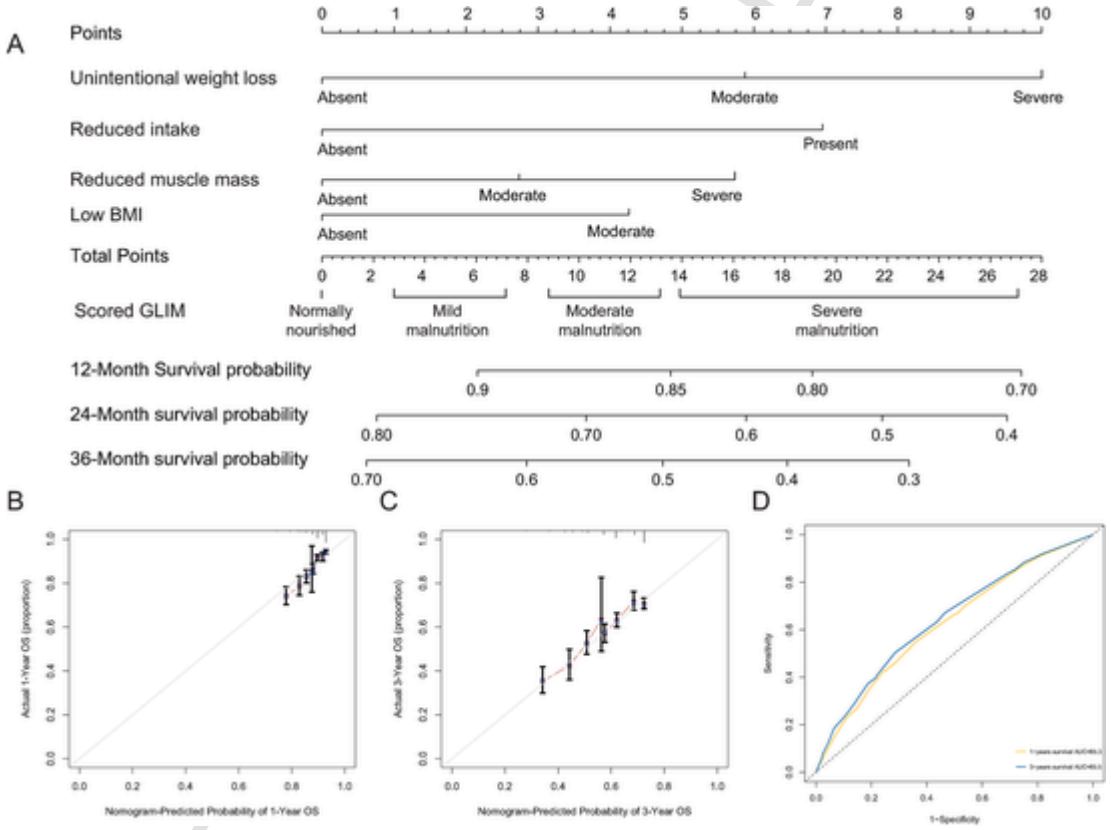

Fig. 3. The nomogram used to quantize the GLIM (A). First, locate the each GLIM criteria site on the axis, then draw a line straight upward to the Points axis to determine how many points the patient receives for the variable. Add the points for each of these predicators together and locate the sum on the Total Points axis to get the scored GLIM. For example, a cancer patient, with unintentional weight loss (>10% within the past 6 months) and reduced intake, but with normal muscle mass and BMI, will be given 10 points for severe unintentional weight loss, 7 points for reduced intake, and 0 point for normal BMI as well as muscle mass. So, the total points of this patient was 17, suggesting a severe malnutrition according to scored GLIM. Calibration curves for primary cohort for the nomogram predictions of the 1-(B)and 3-(C) year overall survival (D)Area under the ROC curves (AUC) for predicting the overall survival at 1, and 3 years in the primary cohort. ROC: receiver operator characteristic. AUC: area under curve.

(Supplementary Fig. 2). The severity of malnutrition based on scored-GLIM showed distinct prognoses (Table 4) and the survival curve was shown in Fig. 4C. After multivariable adjustment of clinical variables and several serum markers, severe malnutrition remained an independent prognostic factor for OS in patients with cancer (Supplementary Table 3). When stratified by tumor type, the severe malnutrition was still associated with worse OS in patients with respiratory system tumors, digestive system tumors and other tumors (supplementary Fig. 3). Multivariate analysis indicated that the severe malnutrition maintained an independent prognostic factor of OS for patients with cancer with different tumor types

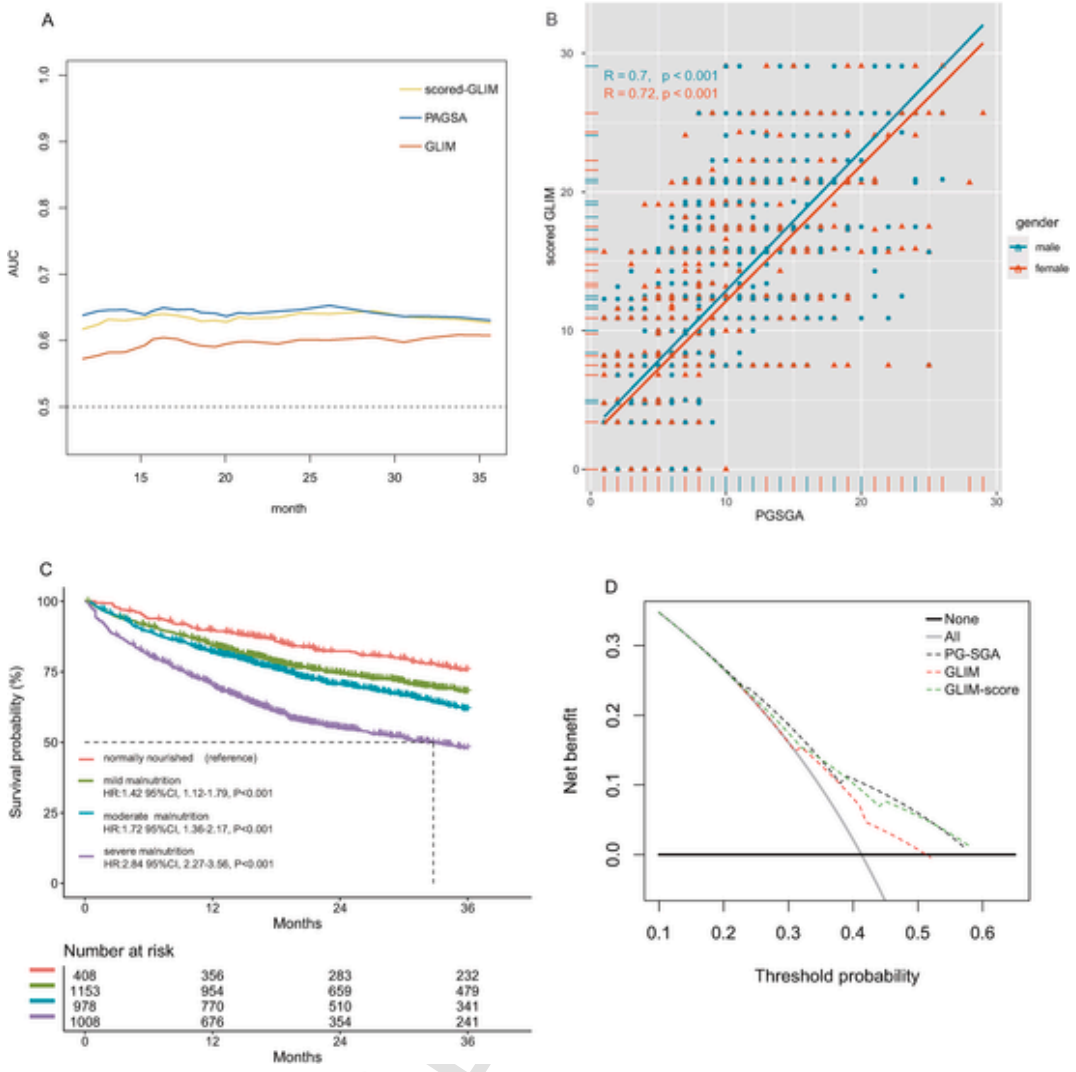

Fig. 4. (A)Time-dependent AUCs over time for scored-GLIM, PG-SGA and GLIM (B) Distribution and correlation between scored-GLIM and PG-SGA among male (blue) and female (red) (C) Kaplan–Meier curve stratified by the scored-GLIM(D) Decision curve analysis on the Scored-GLIM system (green line), model with score-PG-SGA (black line) and GLIM(red line).The gray line denotes the assumption that all patients have outcome event (death) during follow-up. Thick black line represents the assumption that no patients have outcome event (death) during follow-up.

Table 4
Un-adjusted and multivariable adjusted Models for scored-GLIM system.

Scored-GLIM system	Un-adjusted			model 1			model 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Normally nourished	Reference			Reference			Reference		
Mild malnutrition	1.42	1.12–1.79	0.002	1.21	0.95–1.52	0.113	1.27	1.01–1.60	0.043
Moderate malnutrition	1.72	1.36–2.17	<0.001	1.39	1.10–1.75	0.005	1.33	1.06–1.68	0.015
Severe malnutrition	2.84	2.27–3.56	<0.001	2.00	1.59–2.51	<0.001	1.83	1.46–2.30	<0.001

Model 1: adjusted by age and tumor stage. Model 2 adjusted by age, Chemotherapy, tumor stage, Albumin, NLR. NLR: neutrophil-tolymphocyte ratio.

(supplementary table 4). When stratified by TNM stage, the scored GLIM system could allow for identification of a patient with high mortality risk even in spite of the same AJCC TNM stage of cancer (supplementary Fig. 4).

The DCAs for the Scored-GLIM system, scored PG-SGA system, and the conventional GLIM system were presented in Fig. 4D. The decision curve showed that the score-GLIM system had better benefits compared with the model of the conventional GLIM system (the probability threshold is 16% or

higher). In addition, the Scored-GLIM system had similar range of threshold probability (between 22% and 58%) and net benefits with scored PG-SGA system.

4. Discussion

It should be noted that the malnutrition, regardless of the criteria used to define it, is well known to be independently associated with morbidities and mortality [19,20], especially for patients with cancer. Conducting nutritional assessments prior to initiating cancer treatment is imperative no matter what stage the cancer is, the aim is not only to predict the survival but more importantly to improve the prognosis. The Global Leadership Initiative on Malnutrition (GLIM) has recently been launched [10], but it still needs validation studies in specific patient populations. Using the INSCOC cohort, we evaluated the efficacy of the GLIM for diagnosing malnutrition, and found that the GLIM could efficiently assess poor nutrition status which was an independent risk factor for survival. The prevalence of malnutrition was 70.3% which was similar with previously published study [21]. In addition, the Scored-GLIM system showed better performance in identifying a patient with high mortality risk from patients with the same stage of cancer which was clinically useful.

The GLIM framework consisted of all key nutritional criteria information referenced from the most popular assessment tools such as PG-SGA, SGA or screening tools like NRS-2002, MUST and others [19,22,23]. Unintentional weight loss was an important phenotypic criterion that must be considered when carrying out the nutritional status assessment of patients with cancer [24]. In fact, among patients with cancer, weight loss was the first visible or sensible sign, with 40% of the patients reporting that they had lost $>10\%$ of their usual weight when first diagnosed [2]. The criterion of unintentional weight loss was met by 37.9% of our cohort. Moreover, unintentional weight loss contributed the biggest risk of mortality in our cohort after the three years follow-up. A reduced muscle mass was another parameter of the GLIM phenotypic criteria, which was assessed via muscle quantity and muscle function using the AMC, CC and HGS/W [12,25]. The GLIM consensus considered these limb circumference alternative measures for a body composition analysis, in spite of their limitations, and the fact that they were not gold-standard methods for muscle mass estimation [10,26]. Of note, when Stage II malnutrition defined by GLIM was compared with severe malnutrition determined by scored-PGSGA (score≥9), there was a loss of agreement, GLIM defined severe malnutrition was not equivalently diagnosed by PG-SGA, suggesting that the GLIM identify a more severe form of malnutrition than the PG-SGA(Supplementary table 5). The BMI was also proven to be an independent predictor of survival in patients with cancer [27]. Nevertheless, a low BMI had a limited capacity to determine nutrition status [28]. Overweight or obesity were often observed in patients with cancer, even with fluid accumulation, which can mask weight loss and give a false high BMI [13]. In the present study, only 23.96% of subjects were below the established BMI cutoff point. Different symptoms that constituted barriers to dietary intake could be assessed and quantified as symptoms that impacted nutrition [29]. Proper management and identification of nutrition impact symptoms were central parts of the nutritional assessment [30,31]. The amount of nutritional intake and nutrition impact symptoms should be considered when diagnosing reduce intake for GLIM etiologic criteria. In this study, we found that patients with malnutrition experienced more symptoms that impacted nutrition than patients without malnutrition, which the most commons symptoms were loss of appetite (20.8%), pain (13.4%), satiety (11.9%) and nausea (9.7%). Considering the fact that all participants in the current study were suffering from neoplasms, we did not use the severe disease as one of the GLIM etiologic criteria.

Previous studies had reported that different combinations of GLIM were not consistent with the SGA for malnutrition diagnosis [32]. Similar result was also found in the current study. When using all combinations of the two GLIM criteria, 70.34% of patients were diagnosed with moderate/severe malnutrition, whereas PG-SGA identified 83.76% of patients to be moderate/severe malnutrition. After quantizing the GLIM using a nomogram, scored GLIM showed a high consistency with scored PG-SGA, and could reinforce the predictive value of the GLIM, as scored GLIM could even distinguish the prognosis of patients with mild malnutrition (Supplementary table 6). Therefore, this result indicated that using the Scored-GLIM to define and grade malnutrition, as a comprehensive index, might be more valuable for prognostic prediction than using the GLIM criteria.

The main limitation of our study is that all included individuals were patients with cancer, and these patients automatically meet the etiology criterion of the GLIM criteria. Therefore, other parameters, such as inflammatory markers (the C-reactive protein) and other chronic disease burden were not included in the scored GLIM. This may have resulted in the relatively lower efficiency of the GLIM compared to the PS-SGA. In addition, this was a retrospective analysis, the data collection was not designed to validate the GLIM criteria. The assessment of unintentional weight loss and food intake was assessed via self-reporting, and this may have influenced the internal validity of our study. The strength in our study is that it was a multicenter study that could reduce variation in between-hospital causes of admission and in-hospital treatment. As strengths, it should be noted that this is a multicenter study able to reduce variation in between-hospital cause of admission and in-hospital treatment.

In conclusion, our study provides evidence that Scored-GLIM system is an efficient method to identify survival-related malnutrition in patients with cancer. The present study demonstrates that scored-GLIM system is capable of properly identifying a patient with high mortality risk from patients with the same stage of cancer, which may lead to a better “individualized treatment”, and may bring better survival benefits. Cancer staging such as the AJCC TNM classification alone is not powerful enough to design the best treatment plan and therefore the nutritional assessment dedicated to a patient with cancer is imperative. Additionally, scored GLIM showed a similar clinical net benefit compared with the scored PG-SGA, which is the only assessment tool that was specifically developed and validated for the cancer patient population. Together with its obvious time saving and inexpensive advantages, these findings support the use of scored GLIM in clinical practice for patients with cancer.

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Data and materials availability

Approved public trials registries: http://www.chictr.org.cn/showproj.aspx?proj=31813 (ChiCTR1800020329)

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Contributors

HPS conceived and designed the study. QZ,MT, CHS assisted with the methods. QZ, JSDandXZ did the data analysis. QZ and KPZ drafted the initial manuscript. All authors assisted with interpretation, 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 interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.01.033.

Uncited references

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