

Original article

Near-term prognostic impact of integrated muscle mass and function in upper gastrointestinal cancer



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SUMMARY

Background: Despite the known association between muscle mass/function and malnutrition-related mortality in upper gastrointestinal (UGI) cancer, no comprehensive study to determine the impact of muscle mass-dominant nutritional status on cancer prognosis has been conducted. The present study aimed to investigate the prognostic significance of integrated muscle mass and function in UGI cancer.

Methods: Between July 2013 and March 2018, we enrolled 2546 cancer patients with risks of malnutrition (Nutrition Risk Screening 2002, ≥ 3 points) from a multicenter cohort study and split 527 patients with primary UGI cancer into an internal validation group. We prospectively performed instant nutritional assessment and recorded all general clinical characteristics of the participants, such as weight loss, body mass index, anthropometric measurements of muscle mass and function, dietary intake conditions, and disease burden and/or inflammation status based on the validated tools. Prognostic analyses were performed with post-assessment overall survival (OS).

Results: According to the entire set, UGI cancer was identified as the dominant risk factor for disease burden and inflammation criteria (hazard ratio (HR), 2.08, 95% confidence interval (CI), 1.81–2.39, $P < 0.001$). Integrated muscle mass/function analysis with validated cutoff values showed that hand grip strength/weight followed by triceps skinfold thickness and maximum calf circumference are the most potent predictors. Univariate and multivariate analyses revealed that reduced muscle mass/function (74.8%) and dietary intake (66.2%) independently affect OS of patients with UGI cancer. Significant associations were found between the reduced muscle mass/reduced dietary intake and the shortest OS (HR, 4.48; 95% CI, 3.07–6.53; $P < 0.001$). Appending subgroups of muscle mass/function and dietary intake to the pre-existing risk model increased the efficiency of the time-dependent receiver operating characteristic curve analysis for OS in UGI cancer, particularly within 2 years of instant nutritional assessment.

Conclusion: Impaired muscle mass/function adversely affects the near-term prognosis in patients with UGI cancer. Along with a comprehensive evaluation of dietary intake conditions, the timely nutritional assessment might be useful for risk stratification of UGI cancers with potential for enteral and parenteral nutrition interventions.

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1. Introduction

Accurate prognostication of life expectancy is a consequential task for clinical decision-making regarding patient care and enhanced quality of life [1]. Although malnutrition-related outcomes have been reviewed in a number of heterogeneous studies with inconsistent items and standards proposed [2–6], the contributing factors are inseparable from impaired dietary intake or assimilation, declined body composition or physical performance, and metabolic disturbance highlighted by systemic inflammation [7].

Regardless of cancer types, disease burden/inflammation is a widely accepted criterion with significance in clinical diagnosis and prognosis [8–10], for which supportive measurements include physical symptoms and biological indicators, such as ascites, edema, serum C-reactive protein (CRP), and creatinine (Cr) levels [11,12]. Most inflammatory status associated with chronic diseases such as chronic kidney, liver disease, and cancers, could contribute to relevant anorexia, as well as altered metabolism with elevated resting energy expenditure and muscle catabolism [13]. However, in cases of upper gastrointestinal tract (UGI) cancers, such as esophageal cancer, gastric cancer, and pancreatic cancer, the tumor site but not inflammation dominated risk factors for malnutrition-related prognosis, which could be suitable for assessing other aspects, such as muscle mass and dietary intake conditions [14–16].

Manifestations of reduced dietary intake or assimilation are related to unfavorable survival in patients with advanced UGI cancer and are generated by multiple causes, including medication side effects, malabsorptive disorders, and inadequate nutrition support [17,18]. Currently, UGI cancer is associated with chronic gastrointestinal symptoms, such as dysphagia, nausea, vomiting, diarrhea, constipation, and abdominal pain [19,20]. However, the standardized quantity or frequency of each relevant prognostic index remains to be clarified. Accordingly, muscle mass and function are comparatively easy to detect through several measurements [21,22], such as body composition analysis using bioelectrical impedance, dual-energy X-ray absorptiometry or computed tomography, anthropometric examination of the calf or arm muscle circumference, and muscle function assessment by grip strength [23]. Therefore, as an alternative measure, further research is warranted to establish general reference standards for muscle mass and perform adjustments for specific races and sexes.

In this prospective, multicenter cohort study, we integrated the original elements from Patient-generated Subjective Global Assessment (PG-SGA), which comprises features such as weight change, dietary intake, GI symptoms, chronic or acute diseases, anthropometric measures, and physical performance [24,25], to investigate their prognostic accuracy according to a rationale preference in cancer patients with risks of malnutrition. The secondary objective was to compare the predictive accuracy of generalized subgroups based on the selected signatures with the existing risk models comprising tumor-node-metastasis (TNM) stage, surgical excision, PG-SGA, and Karnofsky performance status scale (KPS) [26], in specific UGI cancers as an internal validation.

2. Methods

2.1. Participants with risk of malnutrition

This multicenter, prospective, observational cohort study was performed at the Inpatient Oncology Unit of four hospitals involved in the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project of China (Registration number: ChiCTR1800020329) [27]. Multidisciplinary nutrition support teams provided instant nutrition screening and assessment as part

of standard medical treatment during cancer therapy in those hospitals. All the participants were consecutively included from July 2013 to March 2018 and routinely screened for nutritional risk early in the course of inpatient care. Only those who were identified as “at risk” (≥ 3 points) by the Nutritional Risk Screening 2002 (NRS 2002) [28] were included in this study. Patients who had missing critical values or follow-up visits and those who stayed less than 48 h at the hospital were excluded (Fig. 1). The study was approved by the medical ethical review committees of the registered hospitals mentioned above and was carried out in accordance with the Helsinki Declaration.

2.2. Study design and data collection

In the present study, the age of participants were ≥ 18 years old and both sexes were included (not excluded menopause in relation to women). The patients with extreme values, including albumin < 14 g/L or > 65 g/L, triceps skinfold thickness (TSF) < 2 mm or > 50 mm, maximum calf circumference (MCC) < 14 cm or > 60 cm, were excluded. In total, 2546 patients with general information, medical history, existing comorbidities, anthropometric and laboratory data, physical performance, and follow-up survival information from the initial admission until the endpoint (death or the end of March 2019) were included as an entire set. Then, a total of 527 patients with upper gastrointestinal cancer (esophageal, gastric, pancreatic cancer) were initially split from the entire group as an internal validation set. The medical history along with general characteristics of the population, including age, sex, surgery history, primary cancer types and clinical symptoms, were obtained from electronic medical records according to the International Classification of Diseases, 10th Revision (ICD-10) (Table S1). The pathological stages were determined by the 8th version of the TNM staging system for esophageal [29], gastric, and pancreatic cancer [30].

The accordant nutritional status was assessed as follows. Weight loss was obtained by subtracting the values 6 months prior. BMI was calculated as weight (kg) divided by the height (m) squared (kg/m^2). Muscle mass and function were evaluated by anthropometric measurements, including mid-arm circumference (MAC), triceps skinfold thickness (TSF, nonprof arm), hand grip strength by weight (HGS/W, nondominant hand, CAMRY, Model EH101, Guagndong, China), mid-arm muscle circumference (MAMC, calculated as $\text{MAC (mm)} - 3.14 \times \text{TSF (mm)}$), and maximum calf circumference (MCC, left calf) according to the enteral and parenteral nutritional guidelines and measured by the trainee [31,32].

Dietary conditions regarding reduced food intake over the past 2 weeks, as well as the symptoms of eating problems, including lost appetite, nausea, abdominal pain, constipation, vomiting, dysphagia, diarrhea, depression, dry mouth, oral ulcers, and so on, were evaluated at baseline according to the PG-SGA questionnaires [24,25]. The disease burden and inflammation were evaluated by the combined diseases, including hypertension, diabetes, chronic hepatitis, anemia, osteoporosis, chronic obstructive pulmonary disease (COPD), myocardial infarction, etc., according to the PG-SGA item, as well as the physical examination, such as varying degrees of edema, ascites and trauma. Cancer patients' physical status was assessed by scores on the Karnofsky performance status (KPS) questionnaire [26]. Additionally, serum indicators were obtained from routine measurements on admission, including hemoglobin, leukocyte, and neutrophil count (1 mL blood, Automatic Hematology Analyzer, Sysmex, XE-5000), as well as, creatinine (Cr), total bilirubin (TBil), CRP, serum total protein, and albumin (Bromocresol Green test) (3 mL blood, Beckman Synchron UniCel Dx C 800).

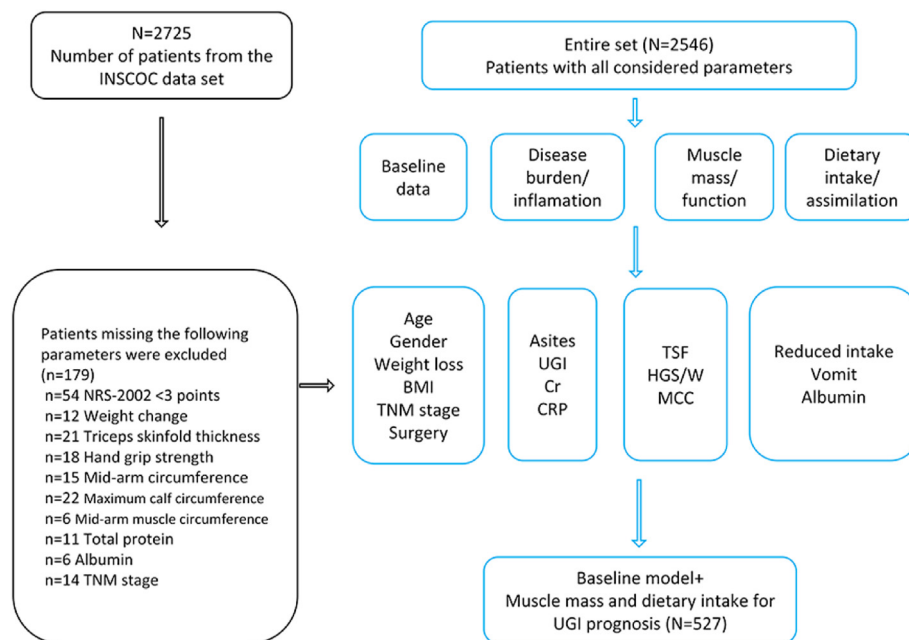


Fig. 1. Study design. INSCOC, the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers; NRS-2002, Nutritional Risk Screening-2002; Weight change, weight changes during the past 6 months; TNM stage, tumor-node-metastasis staging (the 8th version); Surgery, surgical excision; UGI, upper gastrointestinal cancer (gastric, esophageal, and pancreatic cancer); Cr, creatinine; CRP, C-reactive protein; TSF, triceps skinfold thickness; HGS/W, hand grip strength by weight; MCC, maximum calf circumference; Reduced intake, reduced dietary intake > 2 weeks; Albumin, serum albumin.

2.3. LASSO regression for multivariate prognostic model

In the entire set, we applied the least absolute shrinkage and selection operator (LASSO) Cox regression model [33,34] to screen the most significant prognostic factors for each criterion with multiple indicators, such as muscle mass/function, dietary intake, and disease burden/inflammation. According to the machine learning methods performed by the “glmnet” package in R version 3.6.2, a multivariate regression formula was constructed on the basis of the overall survival (OS) time and outcome events. To obtain the final significant prognostic predictors with fewer errors, we analyzed each criterion independently by splitting the data into specific numerical and categorical variables such as symptoms, cancer types and biochemical indexes. The cutoff points of continuous variables were generated by the “survminer” package in R based on the optimal sensitivity and specificity of the receiver operating characteristic (ROC) curve and then used to divide the participants into malnutrition-positive or malnutrition-negative groups.

2.4. Construction of nomograms for the weighted analysis

To predict the prognosis under each malnutrition-associated criterion, we constructed a nomogram that integrated our selected indicators from the entire set. We used the “rms” R package to plot a nomogram for predicting patient OS at 2 years and 5 years. The accuracy of the nomogram was estimated by investigating the consistency index between the actual observations and the predicted probabilities [35]. To avoid model overfitting, we selected the indicators screened by LASSO Cox regression with cross-validation for nomogram model construction. To further gain an accurate estimation of each criterion with multiple indexes, we assigned every chosen indicator a weighted mean according to the score of the nomogram. Kaplan–Meier survival analysis, univariate Cox regression and multivariate Cox regression were further used to assess the survival differences between the favorable and unfavorable groups in each data set through SPSS statistics (IBM, Version 22.0).

2.5. Decision curve analysis for the combined prognostic criteria

To assess the potential effect of combined prognostic criteria according to the Global Leadership Initiative on Malnutrition (GLIM) proposed by the ESPEN experts, we performed decision curve analysis (DCA) to evaluate the efficiency of each combination compared to the total indicators on clinical net benefit. The Kaplan–Meier curve was then applied to verify whether the combined criteria could stratify malnourished cancer patients with distinguished OS times.

2.6. Statistical analysis

Quantitative variables are expressed as the mean $\pm$ standard deviation, and differences were analyzed using Student’s t-test or the Mann–Whitney U test. Categorical data are expressed as frequencies (%) and were tested by Fisher’s exact test or the chi-squared test. Data analysis was performed using R (version 3.6.2, <http://www.rproject.org>; with the “glmnet”, “rms”, “survival”, and “survminer” packages). Additionally, DCA was performed using the source file “stdca.r”, which was downloaded from decision curve analysis.org. Univariate and multivariable Cox proportional OS hazard ratios (HRs) together with 95% confidence intervals (95% CIs) were generated for prognostic factors and other major covariates. Kaplan–Meier curves and Cox regression were used to analyze survival data by the statistical computer program SPSS statistics (IBM, Version 22.0). The level of significance was set at $p < 0.05$.

3. Results

3.1. UGI cancers dominated the risk factors for disease burden and inflammation criteria

In the entire group (Table S1), the age distribution was 58.53 ± 11.25 years, and 57.2% of the patients were male. All the patients showed a varying range of weight loss in the past 6

months, such as less than 5% (71.7%), between 5% and 10% (18.0%) and more than 10% (10.3%). The average BMI values of patients aged <70 years and ≥70 years were 22.83 ± 3.38 and 21.88 ± 3.53 kg/m², respectively. The frequent cancer types were lung cancer (33.6%), colorectal cancer (21.0%), gastric cancer (15.1%), breast cancer (12.4%) and other solid tumors, in which gastric, esophageal, and pancreatic cancers showed extremely poor prognoses.

On the basis of the disease burden and inflammation criterion, we further identified signatures within three categories: chronic diseases, physical symptoms, and biochemical index (Fig. S1). Through LASSO Cox regression analysis performed among multiple significant indicators, we identified ascites, upper gastrointestinal cancer (UGI, including esophageal cancer, gastric cancer, and pancreatic cancer), Cr and CRP as the best prognostic predictors of patients with risks of malnutrition (Fig. 2A). The cutoff values of serum Cr in the entire set were 75.9 μmol/L (male) and 64.9 μmol/L (female) and that of CRP was 2.59 mg/L (Table S2). According to the nomogram of the 2- and 5-year OS, the weighted means of ascites, UGI, Cr, and CRP were identified as 9.0, 10.0, 4.5, and 5.5, respectively, and the survival analysis revealed that the score of distinguishing risk was >9.0 (Fig. 2B–C). Thus, patients with UGI or any two positive indicators showed a significantly worse prognosis (HR 2.08, 95% CI 1.81–2.39, $P < 0.001$) (Fig. 2D).

3.2. Integrated muscle mass and dietary intake criteria contributed to cancer malnutrition

To explore the remaining malnutrition-associated signatures, we performed univariate and multivariate analyses for each criterion with multiple factors. Through LASSO Cox regression analysis and nomograms (Fig. S2A), we confirmed HGS/W as the most potent predictor, followed by TSF and MCC, to represent the muscle mass/function criterion; the cutoff values of each indicator were 0.283, 12.5 mm, and 29.5 cm (male) and 0.468, 11.5 mm, and 30 cm (female), respectively (Table 1). The weighted means of TSF, HGS/W, and MCC were 10, 3.25, and 8, respectively, and the score of distinguishing risk was >11.25 according to the survival analysis (Figs. S2B–C). Therefore, any positive indicator combined with TSF could stratify patients with risks of malnutrition, for whom the integrated positive indicators showed a remarkably unfavorable prognosis (HR 2.67, 95% CI 2.24–3.18, $P < 0.001$) (Fig. S2D).

For dietary intake conditions, the indicators were similarly divided into two categories, symptoms and biochemical indexes, among which “reduced food intake >2 weeks”, “vomiting” and “decreased level of serum albumin” (cutoff value of 31.5 g/L) were identified as the optimal signatures (Table S3). Accordingly, a single indicator of reduced food intake >2 weeks or any two positive indicators could predict unfavorable prognosis.

3.3. Combining muscle mass and disease burden exhibited noninferiority to all elements

To comprehensively analyze the malnutrition-associated criteria, we performed DCA among each crossed group according to the ESPEN guidelines that recommended the combination of at least one phenotypic criterion (weight loss, BMI, and reduced muscle mass/function) and one etiologic criterion (reduced dietary intake, and disease burden and/or inflammation) [13]. The results revealed that muscle mass/function combined with disease/inflammation status (Muscle_Disease) was the most cross-sectional indicator, which approached the efficacy of all indicators (Fig. 3A). The prognosis of each combined group was further investigated and compared with weight loss (HR 1.71, 95% CI 1.48–1.98, $P < 0.001$) or BMI (HR 1.50, 95% CI 1.29–1.74, $P < 0.001$) (Fig. S2). The muscle disease status showed the most remarkable

significance (Fig. 3B), in which the unfavorable group had a worse prognosis with an extremely low median OS time (mOS) (HR 3.63, 95% CI 2.98–4.45, $P < 0.001$, mOS (negative) = 41.52 months, mOS (positive) = 22.20 months). Between the favorable and unfavorable groups, weight loss, BMI values, and serum albumin also varied significantly, which indicated a notable representation of the combining factors (Fig. 3C).

3.4. Value of muscle mass/function as a prognostic factor for UGI cancer prognosis

To particularly assess the internal validation set of UGI cancer, we performed univariate and multivariate Cox regression analyses (Table S4). The integrated muscle mass/function criterion could be identified as an independent indicator, which showed great significance in predicting poor prognosis with a 74.8% positive rate. Importantly, reduced dietary intake was also found to be a significant indicator with a comparatively lower positive rate (66.2%). For the other malnourished indicators, either low BMI or weight loss was not significant in the multivariate Cox regression analysis (Fig. 4A). However, age (>65 years), inoperable and primary site (esophagus and pancreas) corresponded unfavorable prognoses in OS.

We further performed a combination of muscle mass and dietary intake criteria for determining the prognosis of patients with UGI cancer (Table 2). The study population was divided into four groups: normal muscle mass/normal dietary intake group (A, 150 patients, 28.5%), reduced muscle mass/normal dietary intake group (B, 28 patients, 5.3%), normal muscle mass/reduced dietary intake group (C, 244 patients, 46.3%), and reduced muscle mass/reduced dietary intake group (D, 105 patients, 19.9%). Almost no difference was found in age distribution, sex, primary tumor site, and the pathological stage among the subgroups. However, the D subgroup (reduced muscle mass/reduced dietary intake group) showed a considerable decrease in weight loss, BMI values, PG-SGA scores, KPS grades, anthropomorphic parameters of muscle mass/function, and the full evaluation of dietary intake.

3.5. Impact of the near-term prognostic model according to muscle mass/function

To evaluate the predictive stratification by the muscle mass/function and dietary intake criteria in UGI cancer prognosis, the survival analysis for each subgroup was performed. Over a follow-up period of 24 months, a total of 91 (87%) deaths were observed in the reduced muscle mass/reduced dietary intake group (D subgroup), with the Kaplan–Meier curves indicating the shortest OS rate (Fig. 5A). Results of the Cox regression analysis after adjusting for possible confounding factors showed that the risk of mortality was much higher in the D subgroup (adj. HR 3.43, 95% CI 2.16–5.45, $P < 0.001$) (Table S5). Significant interactions were found between subgroups and age ($P < 0.001$), primary site ($P < 0.01$ of pancreatic cancer, 0.003 of esophageal cancer), and surgical resection ($P = 0.046$).

Time-dependent ROC curves were further performed to evaluate the incremental prognostic predictive ability of reduced muscle mass/function and dietary intake in UGI cancer. The AUCs of the baseline model were 0.688, 0.776, and 0.716 for 1-, 2-, and 3-year OS, respectively, which included age, gender, weight loss, BMI values, primary tumor site, surgery and pathological stage (Fig. 5B). To augment nutritional status for prognostic prediction, we compared the baseline model with the addition of model 1 (PG-SGA, KPS grade) or the subgroups (consisting of muscle mass/function and dietary intake) through decision curve analysis (Fig. 5C). As the DCA curve showed, the prognostic efficiency of the

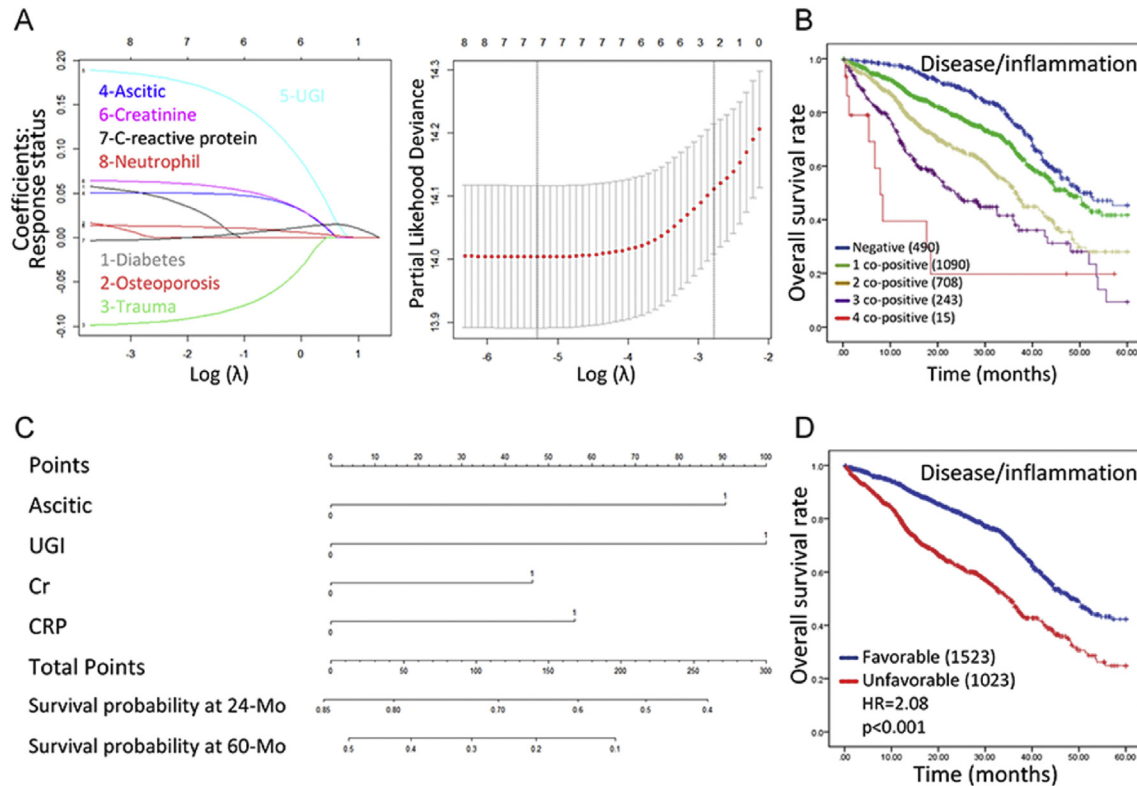


Fig. 2. The significant indicators screened by LASSO Cox regression. (A) Multivariate analysis and cross-validation based on LASSO regression. (B) Kaplan–Meier survival analysis of cancer patients according to the four indicators associated with the disease/inflammation criterion. (C) The weighted averages of ascites (0, 9.0 points), UGI cancer (0, 10.0 points), Cr (0, 4.5 points), and CRP (0, 5.5 points) according to the nomogram for predicting the 5-year overall survival rate. (D) Kaplan–Meier curves for cancer patients with unfavorable (>9.0 points) or favorable status (<=9 points) evaluated by the disease/inflammation criterion (HR 2.08, 95% CI 1.81–2.39, $P < 0.001$). HR, hazard ratio; UGI, upper gastrointestinal cancer (gastric, esophageal, and pancreatic cancer), Cr, creatinine, CRP, C-reactive protein.

Table 1
Indicators of muscle mass and function criteria screened by LASSO Cox regression.

Variables	LASSO Coefficient	Cut-off		Positive Rate ^a	Univariable			Multivariable			Weighted Mean ^b
		Male	Female		HR	95%CI	P value	HR	95%CI	P value	
TSF, mm	−0.042	12.5	11.5	0.339	1.88	1.63–2.16	0.000	1.87	1.61–2.19	0.000	10.00
HGS/W, kg	−1.363	0.283	0.468	0.443	1.04	0.91–1.20	0.542	1.23	1.06–1.42	0.006	3.25
MCC, cm	−0.017	29.5	30.0	0.152	1.98	1.66–2.35	0.000	1.65	1.37–1.98	0.000	8.00

Abbreviation: LASSO, the Least Absolute Shrinkage and Selection Operator; HR, hazard ratio; CI, confidence interval; TSF, triceps skinfold thickness; HGS/W, hand grip strength (kg) by weight (kg); MCC, maximum calf circumference. The significance of bold referred in this article is $p < 0.05$.

^a Positive rate refers to the values below the cutoff that related to unfavorable prognosis.

^b Weighted Mean was decided by the nomogram performed among the indicators.

baseline model + Model 1 was much lower than that of the baseline model + subgroups. Therefore, subgroups based on the evaluation of muscle mass/function and dietary intake were superior to both PG-SGA scores and KPS grade in patients with UGI cancer. The new model containing age distribution, gender, weight loss within 6 months, BMI values, primary tumor site, surgery, pathological stage, and subgroups (consisting of muscle mass/function and dietary intake) could predominantly stratify the near-term prognosis of UGI cancer, with AUCs of 0.761, 0.803, and 0.750 for the 1-, 2-, and 3-year survival rates, respectively (Fig. 5D).

4. Discussion

Nutritional variables are traditionally considered in patients with advanced cancer and included in prognostic models, however, without specific rationale regarding the cancer types [13,36]. We studied a large population with patient-generated and physician-reported outcomes based on the validated nutrition screening

tool. With the thorough sight to evaluate global variables using a robotic statistical approach, we identified integrated muscle mass and dietary intake conditions through validated measures to refine the existing prognostic tools for near-term UGI cancer survival.

4.1. Significance of muscle mass and function for malnutrition-associated prognosis

In the present study, the groups of patients with both reduced muscle mass/function and reduced dietary intake showed a significant association with shorter near-term survival time. Contrary to the conventional tumor-node-metastasis staging and newfound biomarkers, our use of self-reported outcomes and anthropometric data, although some limitations exist, is a strength of the approach. Full-course evaluation is noninvasive, cost-effective and instant for changes in the short term. It is notable that weight loss leads to a reduction in both fat-free mass and fat mass, which further results in decreased muscle strength [37,38], and fat mass is not only a lipid

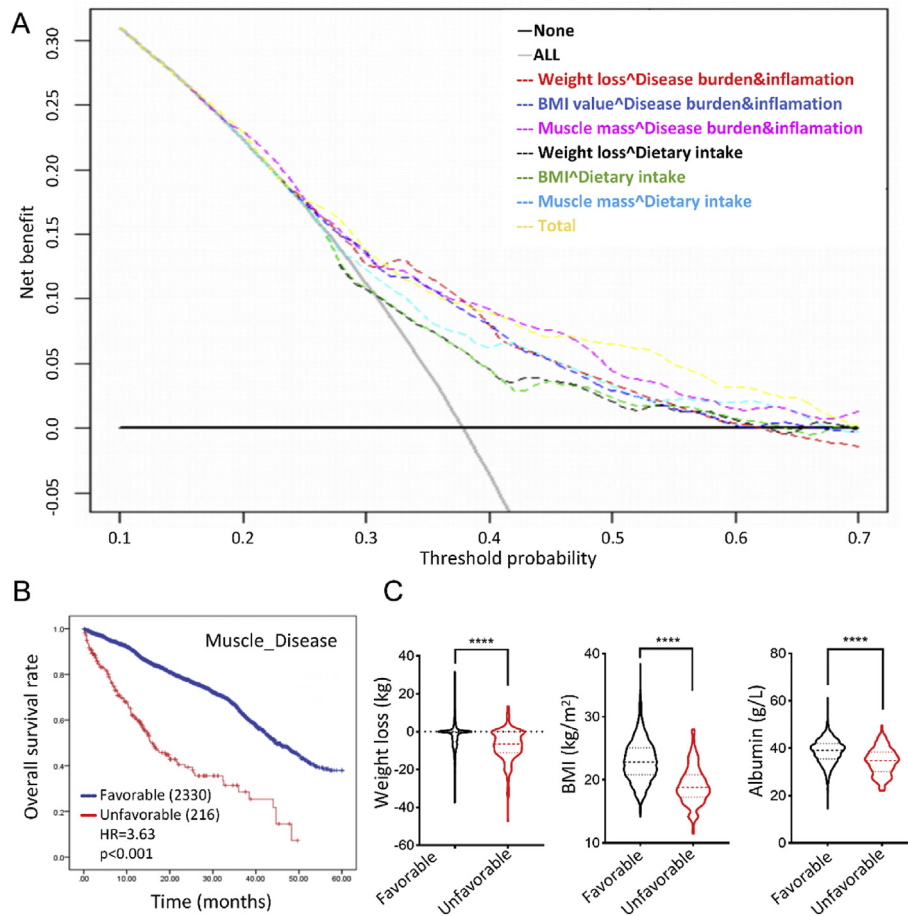


Fig. 3. Combined factors for the stratification of cancer prognosis in the entire set. (A) Decision curve analysis for assessing the potential effect of combined factors on clinical net benefit. (B) The Kaplan–Meier curves for cancer patients with unfavorable (both muscle mass/function and disease/inflammation criteria positive) or favorable status (either muscle mass/function or disease/inflammation criteria negative) (HR 3.63, 95% CI 2.98–4.45, $P < 0.001$, mOS (negative) = 41.52 months, mOS (positive) = 22.20 months). (C) The differences in weight loss within the past 6 months, BMI values, and levels of serum albumin between the favorable and unfavorable groups evaluated by combined muscle mass/function and disease/inflammation criteria. Muscle_Disease, muscle mass/function and disease/inflammation criteria. ****, $P < 0.0001$.

storage depot but also a nutritional reserve that influences the inflammatory and immune response [39,40]. In this study, we found a high prevalence of poor prognosis by integrated indicators, including TSF, HGS/W, and MCC, among which TSF was significantly decreased in 33.9% of cancer patients with risks of malnutrition. A previous study reported that TSF was significantly increased among inpatients who were under controlled protein intake, which had beneficial effects on preserving renal function and nutritional status [41]. Additionally, in situations where muscle mass cannot be assessed, muscle strength is an appropriate supporting proxy [23,42]. HGS is a practical measure of overall muscle function and has been used to indicate frailty. Here, we used the ratio of HGS and weight to eliminate individual differences, and it was found to be decreased in 44.3% of participants by the appropriate cut points for prognosis prediction. HGS could add a significant predictive value for the length of stay and physical quality of life among hospital patients, which will be able to change the course of treatment and intervention [43,44].

4.2. Eating problems add severity to the muscle-reduced malnutrition

Although disease burden and inflammation could impact muscle wasting, we verified a major challenge that impairs the nutritional status in patients with UGI cancer, which is probably

affected due to eating problems caused by the tumor site. We observed potential interactive factors under divided subgroups based on muscle mass/function and dietary intake criteria. To our knowledge, BMI values, as a traditional criterion for malnutrition, still have substantial regional variation and need further investigation in overweight and obese individuals [45–47]. Particularly for underweight patients, it is unreliable to recognize the pace of weight loss early in the course of cancer malnutrition and identify trajectories of decline [48]. Moreover, several forms of weight gain, such as ascites, edema, and increased tumor burden, are the signs of cancer progression [37]. Our results did not necessarily contradict prior studies showing that weight deficits are associated with poor survival; instead, the situations could be simply substituted into reduced muscle mass and/or reduced dietary intake conditions.

4.3. Integrated indicators refined existing prognostic model for UGI cancers

Prognostication for life-limiting illness is a hard enterprise for clinicians, who are often criticized for providing poor estimations to advanced cancers ignoring the discrepancy of individuals. A baseline prognostic model with traditional TNM stage, weight loss, and BMI values has great limitations for cancer survival [49]. For clinical utility, we assessed large population-based data to establish

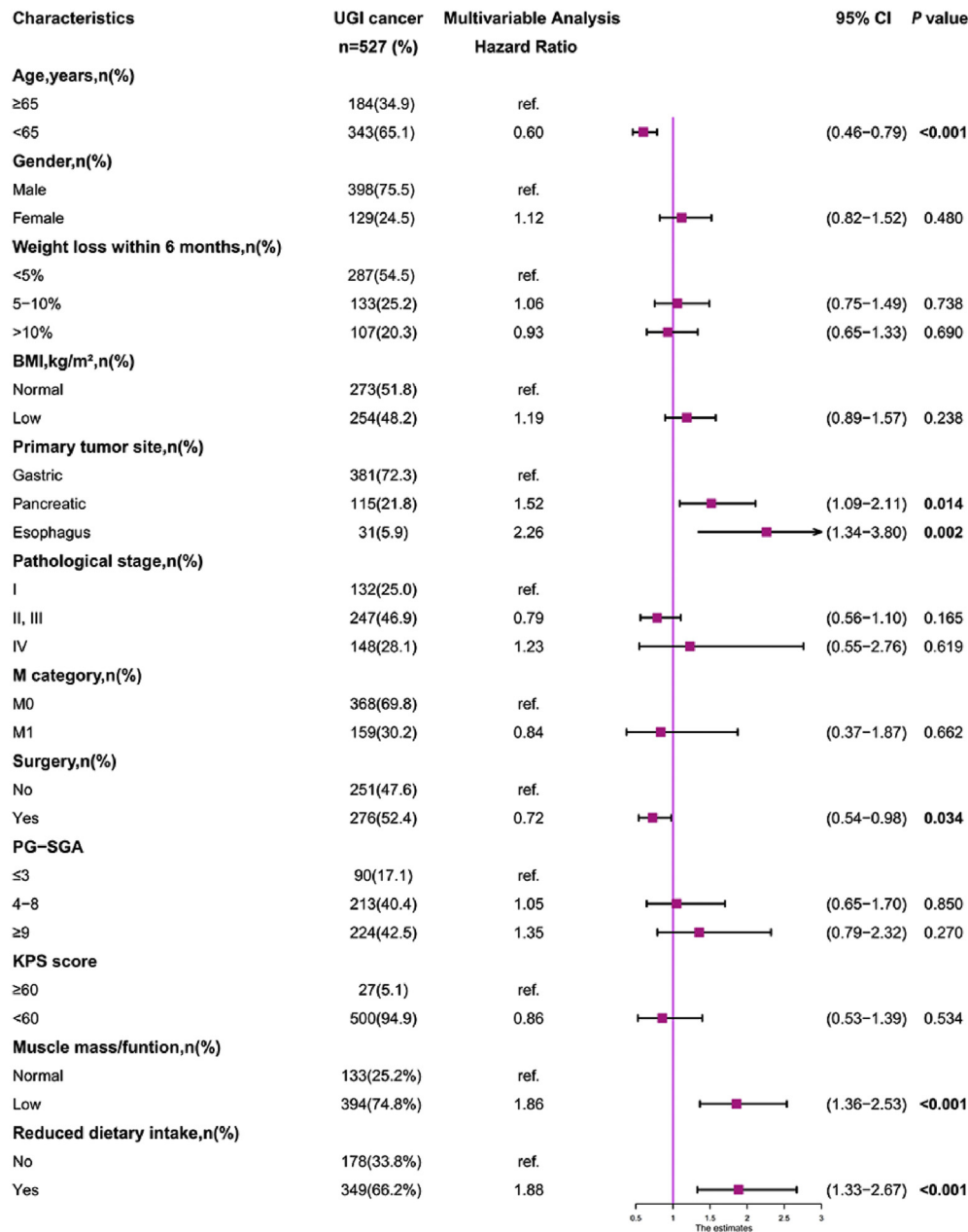


Fig. 4. Multivariate Cox regression analysis based on malnutrition parameters and clinical variables for UGI cancer patients with a risk of malnutrition. BMI, body mass index, M category, metastasis of TNM staging, Surgery, surgical excision, PG-SGA, Patient-Generated Subjective Global Assessment, KPS, Karnofsky performance status scale, Muscle mass/function, normal (≤ 11.25 points) and low (> 11.25 points), evaluated by triceps skinfold thickness (0, 10 points), handgrip strength by weight (0, 3.25 points), and maximum calf circumference (0–8 points); Reduced dietary intake, normal (≤ 9.25 points) and low (> 9.25 points), evaluated by reduced food intake > 2 weeks (0, 10 points), vomiting (0, 8.75 points), and decreased level of serum albumin (0, 9.25 points).

our model, ensuring subgroups consisting of muscle mass/function and dietary intake, which were evaluated by 6 sex-biased indicators with validated cutoff values, and avoiding overfitting estimates of predictive validity. Interestingly, the efficiency of integrated indicators derived from the PG-SGA assessment exhibited an absolute advantage beyond PG-SGA scores and KPS grades. Experts in clinical nutrition have debated the complexity of the PG-SGA tool, which usually owns a certain amount of missing data (2%–15%) [1]. Therefore, valid tools were suitable for collecting data through nutritional screening but not for accurate survival prediction. Our new model comprising muscle mass and dietary intake is potentially valuable for predicting near-term outcomes in patients with UGI cancer, as well as fostering better control of the disease.

4.4. Limitations

An important limitation of this study is that only patients in China were included, although we involved a large population from each age group and gathered data from four hospital sites. Second, the reduced muscle mass was defined only on the basis of anthropometric data, even though we combined it with muscle strength, other comprehensive analyses such as BIA and CT were not performed. In addition, the cut-off values of muscle mass were determined in the entire dataset and validated in the internal dataset; thus, the findings remain to be further verified. Third, this was a prospective cross-sectional study in which limited follow-up information was available for the adaptation of the individualized nutritional intervention. The integrated muscle mass criteria

Table 2
Baseline characteristic of the study population.

Characteristics	ALL	A	B	C	D	P value
	Overall	Normal muscle mass/normal dietary intake	Reduced muscle mass/normal dietary intake	Normal muscle mass/reduced dietary intake	Reduced muscle mass/reduced dietary intake	
	(n = 527)	(n = 150; 28.5%)	(n = 28; 5.3%)	(n = 244; 46.3%)	(n = 105; 19.9%)	
Age, years, mean ($\pm$SD)	59.56 (11.58)	57.80 (10.88)	60.71 (10.85)	59.87 (11.37)	61.04 (12.97)	0.131
Age, < 65 years, n(%)	343 (65.1)	112 (74.7)	15 (53.6)	153 (62.7)	63 (60.0)	0.023
Gender, female, n(%)	129 (24.5)	39 (26.0)	8 (28.6)	52 (21.3)	30 (28.6)	0.437
Weight loss within the past 6 months, n (%)						<0.001
<5%	287 (54.5)	115 (76.7)	18 (64.3)	116 (47.5)	38 (36.2)	
5–10%	133 (25.2)	25 (16.7)	7 (25.0)	73 (29.9)	28 (26.7)	
>10%	107 (20.3)	10 (6.7)	3 (10.7)	55 (22.5)	39 (37.1)	
BMI, kg/m², mean $\pm$ SD	20.81 (3.03)	21.32 (2.75)	17.85 (1.75)	21.69 (2.73)	18.80 (2.98)	<0.001
Primary site, n (%)						0.306
Gastric cancer	381 (72.3)	117 (78.0)	17 (60.7)	176 (72.1)	71 (67.6)	
Pancreatic cancer	31 (5.9)	9 (6.0)	2 (7.1)	15 (6.1)	5 (4.8)	
Esophageal cancer	115 (21.8)	24 (16.0)	9 (32.1)	53 (21.7)	29 (27.6)	
Pathological stage, n (%)						0.393
I	132 (25.0)	40 (26.7)	5 (17.9)	55 (22.5)	32 (30.5)	
II, III	247 (46.9)	75 (50.0)	15 (53.6)	116 (47.5)	41 (39.0)	
IV	148 (28.1)	35 (23.3)	8 (28.6)	73 (29.9)	32 (30.5)	
M category, n (%)	159 (30.2)	38 (25.3)	10 (35.7)	77 (31.6)	34 (32.4)	0.468
Surgery, n (%)	276 (52.4)	90 (60.0)	21 (75.0)	117 (48.0)	48 (45.7)	0.005
PG-SGA, n (%)						<0.001
≤ 3	90 (17.1)	74 (49.3)	6 (21.4)	8 (3.3)	2 (1.9)	
4–8	213 (40.4)	62 (41.3)	15 (53.6)	114 (46.7)	22 (21.0)	
≥ 9	224 (42.5)	14 (9.3)	7 (25.0)	122 (50.0)	81 (77.1)	
KPS, ≥ 60, n (%)	500 (94.9)	150 (100.0)	25 (89.3)	233 (95.5)	92 (87.6)	<0.001
Muscle mass/function, mean $\pm$ SD						
Mid-arm circumference, MAC, cm	25.06 (3.27)	25.73 (2.81)	22.23 (1.82)	26.01 (3.00)	22.63 (3.17)	<0.001
Triceps skinfold thickness, TSF, mm	12.48 (6.06)	13.88 (5.89)	8.05 (2.49)	14.34 (5.99)	7.34 (2.81)	<0.001
Hand grip strength/weight, HGS/W	0.42 (0.15)	0.45 (0.15)	0.43 (0.13)	0.44 (0.14)	0.31 (0.16)	<0.001
Mid-arm muscle circumference, MAMC, cm	21.14 (2.94)	21.37 (2.82)	19.70 (1.84)	21.51 (3.06)	20.32 (2.82)	<0.001
Maximum calf-circumference, MCC, cm	31.75 (3.94)	33.36 (3.46)	28.40 (3.60)	32.70 (2.92)	28.15 (4.01)	<0.001
Reduced food intake or assimilation, n(%)						
Reduction > 2 weeks	341 (64.7)	31 (20.7)	12 (42.9)	205 (84.0)	93 (88.6)	<0.001
Lose appetite	73 (13.9)	4 (2.7)	2 (7.1)	47 (19.3)	20 (19.0)	<0.001
Nausea	50 (9.5)	1 (0.7)	0 (0.0)	30 (12.3)	19 (18.1)	<0.001
Vomit	41 (7.8)	0 (0.0)	2 (7.1)	22 (9.0)	17 (16.2)	<0.001
Constipation	34 (6.5)	4 (2.7)	2 (7.1)	17 (7.0)	11 (10.5)	0.089
Diarrhea	13 (2.5)	4 (2.7)	0 (0.0)	4 (1.6)	5 (4.8)	0.293
Dysphagia	79 (15.0)	12 (8.0)	2 (7.1)	43 (17.6)	22 (21.0)	0.01
Abdominal pain	69 (13.1)	8 (5.3)	3 (10.7)	40 (16.4)	18 (17.1)	0.008
Disease/inflammation, n (%)						
Chronic hepatitis	22 (4.2)	6 (4.0)	0 (0.0)	14 (5.7)	2 (1.9)	0.254
Chronic obstructive Pulmonary disease (COPD)	2 (0.4)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.168
Myocardial infarction (MI)	1 (0.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.472
Diabetes	41 (7.8)	15 (10.0)	2 (7.1)	19 (7.8)	5 (4.8)	0.497
Hypertension	79 (15.0)	19 (12.7)	1 (3.6)	46 (18.9)	13 (12.4)	0.075
Anemia	12 (2.3)	3 (2.0)	0 (0.0)	3 (1.2)	6 (5.7)	0.058
Non-chronic disease	118 (22.4)	33 (22.0)	7 (25.0)	53 (21.7)	25 (23.8)	0.959
Symptoms, n(%)						
Ankles edema	38 (7.2)	5 (3.3)	5 (17.9)	10 (4.1)	18 (17.1)	<0.001
Sacral edema	29 (5.5)	5 (3.3)	2 (7.1)	7 (2.9)	15 (14.3)	<0.001
Ascites	43 (8.2)	6 (4.0)	4 (14.3)	14 (5.7)	19 (18.1)	<0.001
Trauma	27 (5.1)	8 (5.3)	2 (7.1)	13 (5.3)	4 (3.8)	0.887
Laboratory findings, mean $\pm$ SD						
Total protein (TP), g/L	65.44 (7.75)	66.25 (7.04)	65.30 (8.37)	66.24 (7.55)	62.46 (8.39)	<0.001
Albumin, g/L	36.59 (5.17)	38.42 (4.30)	35.84 (5.31)	36.61 (4.75)	34.12 (6.11)	<0.001
Hemoglobin, g/L	117.78 (20.16)	120.32 (18.27)	116.07 (16.58)	119.27 (19.77)	111.16 (23.06)	0.001
Creatinine (Cr), umol/L	74.02 (21.30)	71.80 (18.15)	67.77 (19.65)	75.95 (18.87)	74.37 (29.39)	0.108
Total bilirubin (Tbil), umol/L	15.06 (21.45)	12.06 (5.82)	11.86 (6.86)	14.95 (18.39)	20.47 (37.82)	0.016
C-reactive protein (CRP), mg/L	21.13 (34.69)	14.42 (26.34)	12.00 (17.36)	23.01 (36.08)	28.77 (42.66)	0.004
Leukocyte, 10 ⁹ /L	6.71 (3.01)	6.30 (2.69)	6.28 (2.99)	6.57 (2.62)	7.75 (3.96)	0.001
Neutrophil (NEUT), 10 ⁹ /L	4.57 (2.88)	4.05 (2.50)	4.16 (2.72)	4.41 (2.43)	5.80 (3.93)	<0.001

Abbreviation: SD, standard deviation.

The significance of bold referred in this article is $p < 0.05$.

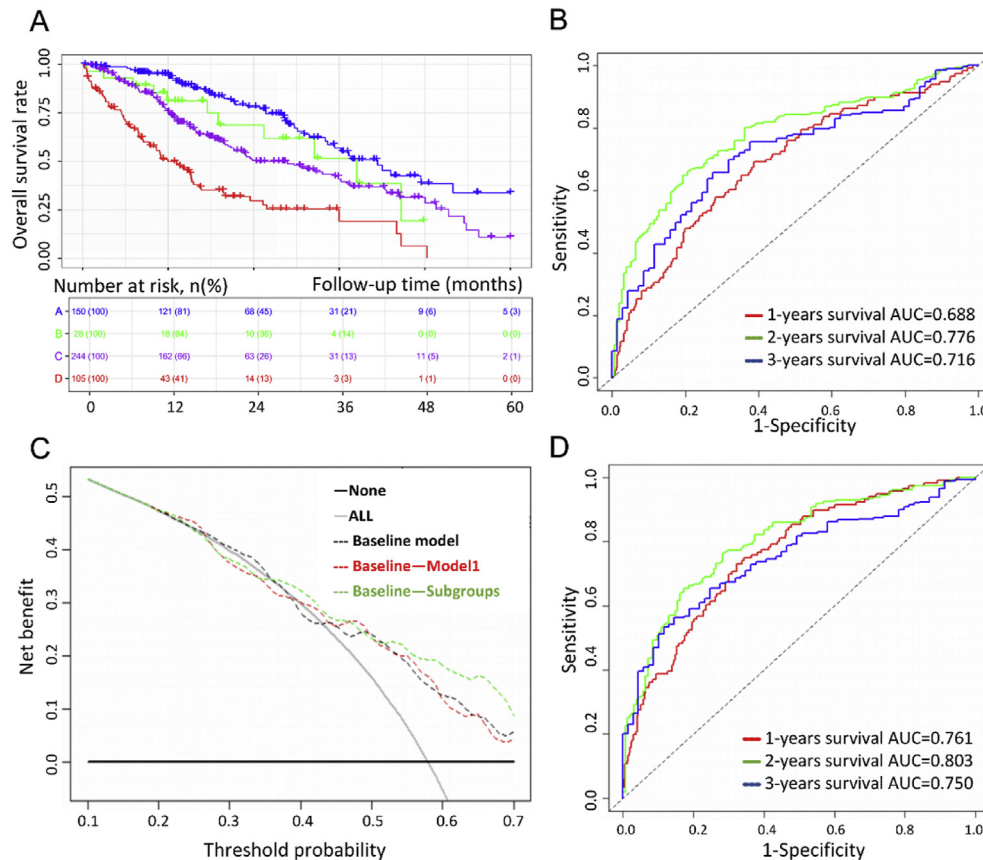


Fig. 5. Prognostic models for the UGI cancer survival. (A) Kaplan–Meier curves for cancer patients in the four groups (HR, 4.48; 95% CI, 3.07–6.53; $P < 0.001$, mOS (A) = 41.37, mOS (B) = 38.47, mOS (C) = 24.37, mOS (D) = 11.97). (B) The ROC curves describing the 1-, 2-, and 3-year survival prognostic efficiency of the baseline model, which involved age, sex, weight loss, BMI values, primary tumor site, surgery or pathological stage. (C) Decision curve analysis for assessing the clinical net benefit of the Baseline model, Baseline model + Model 1, and Baseline + Subgroups. (D) The ROC curves describing the 1-, 2-, and 3-year survival prognostic efficiency of the Baseline model + Subgroups. A, Normal muscle mass/normal dietary intake group (150 patients, 28.5%), B, reduced muscle mass/normal dietary intake group (28 patients, 5.3%), C, normal muscle mass/reduced dietary intake group (244 patients, 46.3%), and D, reduced muscle mass/reduced dietary intake group (105 patients, 19.9%). Model 1, PG-SGA scores, KPS grades, Subgroups, consisting of muscle mass/function and dietary intake.

described in the present study might be relevant to the design of further clinical trials on cancer interventions.

5. Conclusions

This comprehensive analysis of the multicenter cohort study demonstrated the prognostic impact of multi-dimensional malnourishment on patients with cancer. UGI cancer was found to be the main risk factor regarding the entire disease burden and inflammatory indicators. The subgroup analysis of integrated muscle mass/function and dietary intake exhibited an evaluative superiority beyond PG-SGA scores and KPS grades for the UGI cancers, which improved the predictive efficiency of post-assessment overall survival. These results support the instant evaluation of muscle mass/function and dietary intake for patients with UGI cancers, particularly for the prediction of near-term prognosis and controlling of the adverse outcomes. Future studies could further develop and refine the standardized procedures for muscle mass assessments with appropriately verified cut-off values.

Ethics approval and consent to participate

All experimental protocols were first approved by the medical ethical review committee of the First Affiliated Hospital of SunYat-sen University on 2nd January 2013. Then, the study protocol and

procedures were further approved by the local ethical committees of each participating hospitals, including Beijing Shijitan Hospital of Capital Medical University, Zhongnan Hospital of Wuhan University, and National Cancer Center of Chinese Academy of Medical Sciences. Written informed consent was obtained from all participants or, if participants are under 18, from a parent and/or legal guardian.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Authors' contributions

SHP and ZFX conceived and designed the study. TM, GYZ and ZQ analyzed the data and wrote the manuscript. TM, ZQ, XCY, and GYZ drafted the manuscript. ZX, LQQ, ZXW, ZKP, SMM, WX, MY, YM, RGT, HHY, and CMH assisted with the development of the methods. TM, ZQ, and GYZ critically revised the manuscript. All of the authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest

The authors declare that they have no competing interests.

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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.2021.07.028>.

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