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Nutritional assessment tools for identification and monitoring of malnutrition in patients with chronic disease, volume II

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Nutritional assessment tools for identification and monitoring of malnutrition in patients with chronic disease, volume II

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Editorial: Nutritional assessment tools for identification and monitoring of malnutrition in patients with chronic disease, volume II

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Editorial on the Research Topic
Nutritional assessment tools for identification and monitoring of malnutrition in patients with chronic disease, volume II

The European Society for Clinical Nutrition and Metabolism (ESPEN) recognized three different types of malnutrition (or undernutrition), which includes disease-related malnutrition (DRM) with and without inflammation, and malnutrition/undernutrition without disease (1). DRM is highly prevalent among hospitalized patients, with a prevalence rate ranging between 20 and 50% (2). The clinical and economic burden of DRM points out the need for timely identification and treatment of this clinical condition; however, inpatients are not often assessed for DRM, in part due to the lack of standardized criteria for its diagnosis (3–5). Of critical importance is that some common biomarkers, such as serum concentrations of visceral proteins used to assess malnutrition, may not be valid to assess or monitor malnutrition in the context of DRM with inflammation, since they may be affected by the underlying disease-related inflammation process (6).

The Global Leader Initiative on Malnutrition (GLIM) proposed criteria for the diagnosis of malnutrition, including unintentional weight loss, low BMI, and decreased muscle mass as phenotypic criteria, and impaired food intake or assimilation and burden of disease/inflammation as etiologic criteria. To diagnose malnutrition, at least one phenotypic, and one etiological criterion are required; however, criteria for determining inflammation as etiology are not provided, authors only mention that C-reactive protein (CRP), albumin, or pre-albumin could be proxy measures (7). DRM with inflammation according to ESPEN is a catabolic condition triggered by a disease-specific inflammatory response, including anorexia and tissue breakdown (1). Validation studies for the GLIM criteria are still needed to test its validity for the diagnosis of malnutrition in diverse patient populations. Also, sarcopenia should not be considered equivalent to malnutrition but a part of the definition to include skeletal muscle mass and function indicators.

This Research Topic is a second edition of the Nutritional Assessment Tools for Identification and Monitoring of Malnutrition in Patients with Chronic Disease, which addresses the current and novel nutritional assessment tools for the identification and monitoring of malnutrition in patients with chronic disease. In volume 1, a total of 12 articles were included, covering different aspects of malnutrition, such as sarcopenia, its prognosis value, predictor factors, and potential therapeutic strategies, among other relevant topics. Due to the high interest expressed in this Research Topic and the number of meaningful contributions received, volume 2 was released.

In this second edition, 13 articles were published. Eight out of 13 studies provided evidence of the clinical relevance and prognosis value of diverse indexes to screen for nutritional risk and assess malnutrition in different patient populations. Kang et al. showed that the mini nutritional assessment (MNA) screening tool has a better performance to predict various negative outcomes, including 3-month all-cause mortality and geriatric syndrome, compared to serum albumin, one of the biomarkers most commonly used for nutritional assessment, in hospitalized older patients. Another study on the geriatric population conducted by Peng et al. demonstrated that a high risk of malnutrition status identified by the geriatric nutrition risk index (GNRI) was able to predict poor prognosis in elderly patients in the intensive care unit (ICU) setting. The GNRI was also tested along with other nutritional and inflammatory markers for predicting overall survival in early-onset colorectal cancer in a study carried out by Xiang et al.. Authors found that among all nutritional and inflammatory indicators studied, the systemic immune inflammation index (SII) and the GNRI had higher prognostic values, and both were correlated with tumor stage. The prognostic nutritional index (PNI), an indicator of nutritional status and systemic inflammation, was tested for the first time in decompensated liver cirrhosis by Xie et al.. They showed an association between decreased PNI and increased risk of death, suggesting that PNI may be a prognostic marker in this patient population. Also, PNI was identified to be associated with the decision-making on the choice of renal replacement therapy (RRT) modality in adults with advanced chronic kidney disease (ACKD) in a study by Álvarez-García et al.. PNI score was significantly lower in patients who chose home-based RRT (18.8%) compared with in-center RRT (81.2%). However, in the multivariate binary regression analysis, it was not independently associated with the free decision-making to choose in-center and home-based RRT modality but were age, Charlson comorbidity index, follow-up at ACKD unit >6 months, and serum albumin. Chen D. et al. studied the prognostic performance of the Nutritional Risk Screening 2002 (NRS 2002), the Nutrition Risk in Critically Ill (NUTRIC) score, and modified Nutrition Risk in Critically Ill (mNUTRIC) nutritional screening tools that for the first time in patients with severe acute pancreatitis. The three studied scores were predictors for mortality at 28- and 90-days; however, the NUTRIC and mNUTRIC showed better predictive ability in this patient population. In China, the GLIM criteria were modified by removing the muscle-related indicators since these are not based on Chinese population standards. Guo et al. examined the effects of the GLIM-China on the diagnosis of malnutrition in patients with hematopoietic stem cell transplants. Authors concluded that a large proportion of patients with reduced muscle mass indicators will be missed for the diagnosis of malnutrition by using the GLIM-China, highlighting the relevance of muscle mass indicators for the diagnosis of malnutrition.

Two studies addressed the importance of body composition parameters in nutritional status assessment and its role in predicting the risk of clinical conditions. A mini-review by Wu et al. evaluated the role of bioelectrical impedance analysis-derived phase angle as a predictive marker for sarcopenia in patients with cancer and non-cancer diseases, suggesting that phase angle is an emerging and reliable predictor of sarcopenia in patients with different types of cancer; however, its association with non-cancer conditions is less clear. Also, further investigation is needed to determine cutoff values to screen for pre-sarcopenia and sarcopenia. Additionally, Kuang et al. conducted a study to assess the contribution of body composition fat mass (FM) and lean body mass (LBM) to non-alcoholic fatty liver disease (NAFLD), demonstrating higher LBM is associated with a lower risk of NAFLD and higher FM increasing the risk of this condition, particularly in women. Undoubtedly, body composition analysis represents a key aspect of nutritional status assessment; however, any nutritional assessment needs to guide a decision-making process to manage malnutrition when identified. In this sense, in a retrospective study of patients with Crohn's disease, Jiang et al. confirmed that pre-operative nutritional status correlates with post-operative outcomes and that enteral nutrition was associated with an improvement in nutritional parameters and a reduced rate of postoperative complications in patients with Crohn's disease undergoing surgery.

Evidence on the usefulness of other technologies such as 3D facial image recognition was also provided in this Research Topic. Chen M. et al. reported that the facial temporal region and periorbital depression indicators extracted by 3D image recognition technology were associated with the phenotype of malnutrition-related muscle and fat loss in patients with cancer, providing an alternative for a clinical auxiliary tool for malnutrition screening and assessing phenotypic indicators of malnutrition.

Finally, Domenech-Briz et al. contributed with a systematic review of 14 the importance of nutritional assessment tools in critically ill patients pointed out the benefits of screening or assessing malnutrition for predicting mortality risk and early initiation of nutritional therapy, reducing the number of complications and length of stay related to malnutrition or adjusting energy requirements. Authors concluded that among the studied tools, the most widely used and effective were the modified Nutrition Risk in the Critically Ill (mNUTRIC) score, the Nutrition Risk Screening 2002, and the Subjective Global Assessment, either independently or in combination with each other.

In conclusion, further studies are needed to demonstrate that in addition to the identification of DRM, with above mentioned nutritional assessment tools, nutritional and exercise interventions are justified, and changes in nutrition outcomes could be detected after these interventions. It is crucial to include a decision-making process to guide the management when malnutrition is present.

Author contributions

EC-R wrote the introduction and central part with comments on the cited papers and references. LC-M wrote the conclusion and reviewed/edited the introduction and central part. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The association of Carbohydrate Quality Index with cardiovascular disease risk factors among women with overweight and obesity: A cross-sectional study

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Purpose: Diet is one of the most important factors influencing cardiovascular disease (CVD). The negative relationship between carbohydrate intake with lipid profiles and body weight has been previously investigated. However, this is the first study seeking to assess the association of carbohydrate quality index (CQI) with CVD risk factors.

Methods: This cross-sectional study was conducted on 291 Iranian overweight and obese women, with a body mass index (BMI) ranging between 25 and 40 kg/m^2, and aged 18–48 years. CQI scores were calculated by using a validated 168-item semi-quantitative food frequency questionnaire (FFQ). Biochemical and anthropometric measures were assessed using standard methods, and bioelectrical impedance was used to measure body composition.

Results: We observed that fruits ($P < 0.001$), vegetables ($P < 0.001$), and protein ($P = 0.002$) intake were higher in participants with a higher score of the CQI. When we adjusted for potential confounders, we observed that the CQI was negatively related to systolic blood pressure (SBP) ($\beta = -6.10$; 95% CI $= -10.11$, -2.10; $P = 0.003$) and DBP ($\beta = -3.11$; 95% CI $= -6.15$, -0.08; $P = 0.04$). Also, greater adherence to a high CQI dietary pattern, compared to the reference group, was negatively related to HOMA-IR ($\beta = -0.53$; 95% CI $= -0.94$, -0.12) (P for trend $= 0.01$), WC ($\beta = -3.18$; 95% CI $= -6.26$, -0.10) (P for trend $= 0.04$), BMI ($\beta = -1.21$; 95% CI $= -2.50$, 0.07) (P for trend $= 0.06$), and BF ($\beta = -2.06$; 95% CI $= -3.82$, -0.30) (P for trend $= 0.02$).

Conclusion: In line with previous studies, the CQI was inversely associated with blood pressure, WC, BMI, and BF. Further prospective and clinical trial studies are suggested to confirm these data.

KEYWORDS

cardiovascular disease risk factors, anthropometric measures, body composition, obesity, carbohydrate quality index

Introduction

Obesity is one of the most profound medical problems in the world that increases the risk of other chronic diseases, such as cardiovascular disease, cancers, and diabetes (1). According to the World Health Organization (WHO), more than 1.9 billion adults, over 18 years, were overweight in 2016, and more than 650 million of them were obese (2, 3). It is estimated that, by 2030, 2.5 billion people will be overweight or obese (4, 5). Women appear to be more affected by the obesity epidemic than men, where this difference may be related to nutrition, lifestyle, behavior, sexual, and environmental differences (6, 7). Moreover, a higher risk of cardiovascular disease (CVD) in women has been observed, especially in women with obesity or overweight (8–10). Factors influencing the incidence and prevalence of obesity include genetic and environmental factors, such as lifestyle and eating habits (11, 12). Further diet is one of the most important factors influencing chronic inflammatory conditions (13).

Special diets have been suggested for the maintenance of optimal body weight. However, their results are controversial (14). Some studies have investigated the role of macronutrients, especially carbohydrates as the main source of energy by Iranians, in the development of obesity (14). Accordingly, low carbohydrate diets (LCD) were reported as a common weight-loss strategy (15). Interestingly, a systematic review showed no association between high carbohydrate intake with the risk of obesity (16). The results of one trial revealed that the LCD may reduce body mass and fat content (17); however, they did not consider the calorie intake and carbohydrate quality (18). The quality of dietary carbohydrates may be more important than their quantity in reducing the risk of CVD (19, 20). Also, one factor alone is insufficient to predict the association between carbohydrate intake with obesity risk, and so, carbohydrate quality should be determined by considering several important factors simultaneously (18). Thus, Carbohydrate Quality Index (CQI) was defined in which fiber intake, glycaemic index (GI), whole grains/total grains ratio, and solid carbohydrate/total carbohydrate ratio are calculated (21). In a cohort study, a negative relationship between CQI with obesity was shown (22). Another study proposed that CQI components, such as GI, significantly affected abdominal obesity (23). Moreover, a previous study concluded that fiber intake elicited weight-loss and body fat (BF) loss, compared to refined grains (24). Also, a low GI diet may be associated with a decrease in body fat mass (BFM) (25, 26).

The association between obesity with CVD in men was reportedly related to high blood pressure and cholesterol (27, 28). Thus, controlling these two factors can be effective in reducing the risk of CVD. The results of prospective cohort studies have shown that each 5 kg/m^2 higher body mass index (BMI) is associated with a 27% higher risk of chronic heart disease (29). A cohort study showed an increment in high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and total cholesterol (TC) in obese participants (30). Moreover, a meta-analysis demonstrated LCD can lead to a decrease in body weight, waist circumference (WC), BMI, TG, and blood pressure (31). A positive relationship between CQI with HDL levels was observed in a study (32). In a Mediterranean cohort study, an inverse relationship was observed between better CQI with the incidence of CVD (33). In another study, the CQI had a positive relationship with HDL levels, and a negative relationship with systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, and WC (34).

Several mechanisms have been proposed for these relationships, including the association of high GI foods with hyperinsulinemia, increased fat storage, and reduced blood glucose fluctuations, which leads to increased appetite and food intake (35–37). Fiber intake decreases appetite through slowing

Abbreviations: ANCOVA, Analysis of Covariance; ANOVA, Analysis of Variance; BF, body fat percentage; BFM, body fat mass; BMI, body mass index; CIs, confidence intervals; CHO, carbohydrates; CVDs, cardiovascular diseases; CQI, carbohydrate quality index; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FBS, fasting blood sugar; FFM, fat-free mass; FFMI, fat free mass index; FFQ, food frequency questionnaires; FMI, fat mass index; HC, hip circumference; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IPAQ, International Physical Activity Questionnaire; LCD, low carbohydrate diet; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; N, number; NC, neck circumference; PA, physical activity; PUFA, polyunsaturated fatty acids; SBP, systolic blood pressure; SD, standard deviation; T, tertile; TC, total cholesterol; TG, triglyceride; TF, trunk fat; TUMS, Tehran University of Medical Sciences; VFA, visceral fat area; VFL, visceral fat level; WC, waist circumference; WHO, world health organization; WHR, waist-hip ratio.

stomach emptying and hormone signaling, and decreases postprandial insulin that increases lipid oxidation (38–42), whilst high liquid carbohydrate intake increases appetite and postprandial blood glucose and decreases insulin sensitivity (43, 44), and whole grains can reduce the digestion and absorption of starch and appetite (38, 45).

To our knowledge, there is no previous study investigating the relationship between CQI with CVD risk factors in Iranian women. Therefore, due to the high prevalence of CVD and its importance, we intended to determine the relationship between CQI and CVD risk factors among women with overweight and obesity.

Materials and methods

Study population

This cross-sectional study was conducted on 291 overweight and obese women, aged 18–48 y, who were recruited from health centers in Tehran, Iran. The BMI of women ranged between 25 and 40 kg/m^2. Exclusion criteria included: history of any chronic diseases such as diabetes mellitus, hypertension, CVDs, liver or kidney diseases, taking all types of medicine including birth control pills, smoking, intake of alcohol, pregnancy, lactating women, post-menopause, body weight changes in the last year, weight-loss diets or an arbitrary special dietary regimen, and chronic disease that affected their diet. All participants signed a consent form before starting this study. Our study was approved by the local ethics committee of the Tehran University of Medical Sciences. The approval number was IR.TUMS.MEDICINE.REC.1400.182.

Assessment of dietary intake and CQI calculation

A reliable semi-quantitative food frequency questionnaire (FFQ) was used for obtaining the usual dietary intake of participants during the past year. This FFQ included 168 items, where standard portion size, and food frequency categories (daily, weekly, monthly, and yearly) for each food which was converted to grams per day using household measurements (46). This FFQ was collected with a face-to-face interview by a trained interviewer, and Nutritionist-4 software was used to analyze the data.

The area below the glycemic response curve for each participant based on the reference food was shown as a percentage of the average area under the curve, after each food. Food GI for all participants was calculated by mean of these values. White bread was used as a reference food. GI values were multiplied by 0.71 to convert the glucose scale (i.e., GI glucose = 100) (47). Total GI was estimated using the following formula: (GI × available carbohydrates)/total available carbohydrates. To calculate available carbohydrates, fiber was deducted from total carbohydrates, which were derived from the United States Department of Agriculture food composition databases (48).

CQI was computed by summing the following four criteria: dietary fiber intake (g per day), GI, the ratio of whole grains to total grains, and the ratio of solid carbohydrate to total carbohydrate. Total grains include whole grains, refined grains, and their products. For each of these four components, a score of 1–5 was considered. Finally, CQI is obtained and ranges from 4 to 20; participants were subsequently categorized into tertiles (28).

Anthropometric measurements and body composition analysis

Weight was measured on a digital scale, where participants were weighed with minimal clothing and without shoes, to the nearest 100 g. Participants' height was measured, without shoes, to the nearest 0.5 cm. WC and hip circumference (HC) were measured to the nearest 0.5 cm, according to standard procedures. Subsequently, waist-to-hip ratio (WHR) and BMI were calculated according to standard formulae. According to WHO guidelines, overweight and obesity were defined as $25 \leq$ BMI ≤ 29.9 kg/m^2 and BMI ≥ 30 kg/m^2, respectively. Neck circumference (NC) was measured by the use of non-stretchable plastic tape, to the closest 1 mm, just underneath the laryngeal prominence perpendicular to the long axis of the neck with the head placed within the Frankfort horizontal aircraft (49). The body composition of participants was measured by a Body Composition Analyzer BC-418MA- In Body (United Kingdom), according to manufacturer guidelines. Participants were asked not to exercise, not to use any electrical devices, and not to consume excessive fluid or food before measuring the body composition, to prevent any discrepancies in the measured values.

Biochemical assessment

After 10–12 h of fasting at night, a blood sample was drawn and serum was collected into tubes containing 0.1% Ethylenediaminetetraacetic acid (EDTA). Then, they were centrifuged for 10 min at 3,000 rpm, aliquoted into 1 ml tubes, and stored at −70°C until analysis. Sample analysis was performed by using an autoanalyzer (Selectra 2; Vital Scientific, Spankeren, Netherlands). The FBS was measured by using the GOD/PAP (glucose oxidase phenol 4-Aminoantipyrine Peroxidase) method. The serum levels of HDL and LDL were determined by turbidimetry on a Roche Hitachi analyzer (Roche, Germany). The blood levels of TG and TC were determined by using an enzymatic technique and commercially

available Pars Azmoon, Iran kits. Also, a high-sensitivity immunoturbidimetric assay (Hitachi 902 analyzer; Hitachi Ltd, Tokyo, Japan) was used to measure serum high-sensitivity C-reactive protein (hs-CRP). Furthermore, the homeostasis model assessment method was used to determine insulin resistance *via* the HOMA-IR formula as follows: fasting serum insulin (mlU/L) × FBS (mmol/L)/22.5 (50). HOMA-IR cut-off values > 2.63 are considered as the presence of insulin resistance (51).

Blood pressure assessment

The blood pressure of participants was measured by a standard mercury sphygmomanometer (ALPK2 k2-232; Japan), while the participants were sitting for 10–15 min, before performing two consecutive measurements. Two measurements were performed at 1 min intervals and the average was considered.

Physical activity

Participants' physical activity was assessed by the short form of the international physical activity questionnaire (IPAQ), according to the frequency and time of common activities of daily life over the past year. Physical activity levels were expressed as metabolic equivalent minutes per week (MET-minutes/week) (52) and were divided into categories as follows: very low (<600 MET-min/week), low (600–3,000 MET-min/week), moderate, and high (>3,000 MET-min/week) (53).

Assessment of other variables

A demographic questionnaire was used to collect information about age, marital status, education, occupation, economic status, and supplementation.

Statistical analysis

The minimum sample size was 152 people through the following formula and with a design effect of 1.5: $n = (([(Z_{1-\alpha} + Z_{1-\beta}) \times \sqrt{1 - r^2}]/r)^2 + 2)$, which $\alpha = 0.05$, $\beta = 0.95$, $r = 0.3$ (54). Quantitative variables were described as mean and standard deviation (SD) and categorical variables were described as numbers and percentages. The Kolmogorov-Smirnov test was used to check the distribution of data ($P > 0.05$, indication normal distribution). All statistical analyses were performed by SPSS software version 26, and $P < 0.05$ was considered to be statistically significant, and $P = 0.05$–0.07 was considered marginally significant. By use of the NOVA score, participants were categorized into tertiles. Individuals in tertile 1 were 103 (35.4%) with a threshold of <10, in tertile 2 were 99 (34%) with a threshold of 10–13, and 89 (30.6%) for tertile 3 with a threshold of >13. To compare the mean difference of quantitative variables and percent of categorical variables across NOVA tertiles, one-way analysis of variance (ANOVA) and chi-square (χ^2) tests were performed, respectively. Analysis of covariance (ANCOVA), controlling for potential confounders (age, BMI, energy intake, and physical activity) and considering BMI as a collinear variable for anthropometric measures and body composition variables, was also conducted. Bonferroni *post-hoc* testing was done to identify the exact location of significant mean differences among tertiles, if necessary. Linear regression was conducted to determine the association between CQI and CVD risk factors. Model 1 was adjusted for age, BMI, energy intake, and physical activity, and Tertile 1 was considered as the exposure reference group. The results were reported as β, with a 95% confidence interval (95% CI).

Results

Study population

This cross-sectional study was conducted on 291 overweight and obese women, of whom, 72.2% were married, 97.9% were employed, 48.8% had a college education, and 23% had a poor economic level. The mean (SD) of age, weight, BMI, and WC of participants was 36.51 (8.51) years, 80.71 (12.22) kg, 31.05 (4.32) kg/m^2, and 98.96 (10.04) cm, respectively. Also, the mean (SD) CQI of participants was 11.83 (3.12). Other main demographic quantitative and qualitative variables are shown in Table 1.

General characteristics of study participants among tertiles of the CQI

Based on Table 2, the participants with a higher score of CQI were older ($P = 0.002$). Although the participants with a higher score of CQI had a lower mean weight, there was no significant difference between the anthropometric measures and other general characteristics of participants across tertiles of CQI ($P > 0.05$).

Dietary intake of study participants among tertiles of the CQI

As shown in Table 3, energy ($P = 0.01$), protein ($P = 0.002$), and carbohydrate ($P = 0.001$) intake were higher in participants with a higher score of the CQI and total fat intake was lower after controlling for potential confounder (energy intake) ($P < 0.001$). participants with a higher score of CQI had a significantly lower intake of saturated fatty acids (SFA), and a

TABLE 1 General characteristics of the study participants ($n = 291$).

Variables	Mean	SD	Minimum	Maximum
Demographics				
Age (years)	36.519	8.511	17	56
PA (MET-minutes/week)	998.39	1,089.26	10	7,296
Blood parameters				
FBS (mg/dl)	87.49	9.62	67	137
TC (mg/dl)	185.15	36.25	104	344
TG (mg/dl)	118.30	59.78	37	328
HDL (mg/dl)	46.80	10.85	18	87
LDL (mg/dl)	95.03	24.19	34	156
hs-CRP (mg/L)	4.31	4.65	0.00	22.73
Blood pressure				
SBP (mmHg)	111.65	13.75	76	159
DBP (mmHg)	77.77	9.62	51	111
Anthropometric parameters				
Weight (kg)	80.71	12.22	59.50	136.60
Height (cm)	161.28	5.93	142	179
BMI (kg/m^2)	31.05	4.32	24.20	49.60
WC (cm)	98.96	10.04	80.10	136
WHR	1.24	5.34	0.81	0.92
HC (cm)	114.14	9.75	100	160
NC (cm)	37.56	7.39	31	134.5
Body composition				
FFM (kg)	46.78	5.58	35.30	63
BFM (kg)	34.01	8.67	19.40	74.20
BF (%)	41.51	5.53	15	54.30
VFA (cm^2)	168.28	104.83	20	1,817
VFL (cm)	16.66	14.17	7	208.4
FFMI	18.40	7.78	14.6	147.8
FMI	13.15	3.39	6.9	26.9
TF (kg)	16.56	3.70	9.7	30.2
TF (%)	313.74	70.02	177.8	536.6
CQI components				
CQI	11.83	3.12	4	19
Fiber (g/day)	41.00	14.35	8.61	87.89
Glycaemic index	56.75	6.13	40.50	67.69
Solid CHO (g/day)/ total CHO (g/day)	0.71	0.21	−0.75	1
Whole grain (g/day) to total grain (g/day)	0.02	0.03	0.00	0.31
HOMA-IR index	3.34	1.28	1.29	9.19
Categorical variables	**Status**	***N***	**%**	
Marriage status	Single	87	26.8	
Occupation	Unemployed	2	0.7	
Education	Illiterate	3	1	
	Under diploma	36	12.4	
	Diploma	107	36.8	
	Bachelor and higher	142	48.8	
Level of economic status	Poor	67	23	
	Moderate	138	47.4	
	Good	72	224.7	
Supplementation	Yes	134	46	

(Continued)

TABLE 1 (Continued)

BF, body fat percentage; BFM, body fat mass; BMI, body mass index; CHO, carbohydrates; CQI, carbohydrate quality index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FFM, fat-free mass; FFMI, fat-free mass index; FMI, fat mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; N, number; NC, neck circumference; PA, physical activity; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; TF, trunk fat; VFA, visceral fat area; VFL, visceral fat level; WC, waist circumference; WHR, waist-hip ratio.
Quantitative variables were obtained from one-way ANOVA and presented as mean ± SD, and qualitative variables were obtained from the Chi-Square test and presented as frequency and percentage.

higher intake of vegetables, legumes, whole grains, potassium, calcium, phosphorus, iron, magnesium, copper, vitamin K, vitamin B1, vitamin B2, vitamin B6, vitamin B8, and vitamin B9 consumption after adjusting for energy intake ($P < 0.001$). In addition, these differences were significant for fruits ($P = 0.003$), nuts ($P = 0.06$), total fiber ($P = 0.01$), zinc ($P = 0.007$), vitamin A ($P = 0.001$), vitamin C ($P = 0.03$), vitamin B3 ($P = 0.003$), and pantothenic acid ($P = 0.01$) intake. Monounsaturated fatty acids (MUFA) ($P < 0.001$), polyunsaturated fatty acids (PUFA) ($P = 0.06$), and linoleic acid ($P = 0.04$) intake were lower in participants with a higher score of CQI after energy intake controlling. However, there was no significant mean difference between the other dietary components intake of participants across tertiles of the CQI ($P > 0.05$).

CVD risk factors, anthropometric measures, and body composition of study participants among tertiles of the CQI

In the crude model, HOMA-IR ($P = 0.003$) and BF ($P = 0.01$) were significantly lower in participants with higher adherence to a high CQI diet, and DBP ($P = 0.06$) and BFM ($P = 0.06$) are marginally significantly lower in participants with higher adherence to a diet with high CQI. However, after adjusting for age, BMI, energy intake, and physical activity, HOMA-IR ($P = 0.007$), WC ($P = 0.02$), WHR ($P = 0.007$), BFM ($P = 0.02$), BF ($P = 0.01$), fat mass index (FMI) ($P = 0.01$), trunk fat (TF) (kg) ($P = 0.01$), and TF (%) ($P = 0.009$) were significantly lower and BMI ($P = 0.06$) is marginally significantly lower in participants with consumption of high CQI diet. There was no significant mean difference between the other CVD

TABLE 2 General characteristics of study participants among tertiles of the CQI ($n = 291$).

Characteristics		Tertiles of CQI			*P*-value*	*P*-value**
		T1 $n = 103$ Mean ± SD <10	T2 $n = 99$ Mean ± SD 10–13	T3 $n = 89$ Mean ± SD >13		
Demographics						
Age (years)[a]		34.51 ± 9.14	37.22 ± 8.68	38.06 ± 7.09	**0.009**	**0.002**
PA (MET-minutes/week)		884.59 ± 731.34	938.46 ± 1,024.15	1,160.41 ± 1,407.53	0.24	0.07
Anthropometric parameters						
Weight (kg)		82.33 ± 14.09	80.28 ± 11.94	79.31 ± 9.90	0.21	0.47
Height (cm)		161.41 ± 5.62	160.70 ± 5.93	161.78 ± 6.26	0.44	0.66
HC (cm)		115.33 ± 12.02	113.04 ± 8.41	113.83 ± 7.62	0.43	0.99
Insulin (mlU/ml)		1.20 ± 0.25	1.21 ± 0.22	1.23 ± 0.20	0.76	0.54
Categorical variables			***N* (%)**			
Marriage status	Single	23 (29.5)	30 (38.5)	25 (32.1)	0.41	0.29
	Married	79 (37.6)	68 (32.4)	63 (30.0)		
Occupation	Unemployed	1 (50.0)	0 (0.0)	1 (50.0)	0.75	0.58
	Employed	101 (35.4)	98 (34.4)	86 (30.2)		
Education status	Illiterate	2 (66.7)	1 (33.3)	0 (0.0)	0.81	0.66
	Under diploma	15 (41.7)	13 (36.1)	8 (22.2)		
	Diploma	36 (33.6)	36 (33.6)	35 (32.7)		
	Bachelor and higher	49 (34.5)	48 (33.8)	45 (31.7)		
Level of economic status	Poor	21 (31.3)	22 (32.8)	24 (35.8)	0.27	0.91
	Moderate	49 (35.5)	54 (39.1)	35 (25.4)		
	Good	28 (38.9)	19 (26.4)	25 (34.7)		
Supplementation	Yes	44 (32.8)	46 (34.3)	44 (32.8)	0.80	0.99
	No	37 (37.0)	32 (32.0)	31 (31.0)		

HC, hip circumference; N, number; PA, physical activity; SD, standard deviation; T, tertile.
Participants were divided into categories called tertiles.
*The *P*-values were obtained by the use of ANOVA or the Chi-Square test.
**The *P*-values were obtained by the use of ANCOVA after adjustment for age, BMI, energy intake, and physical activity (MET-minutes/week). BMI is considered a collinear for anthropometric measurements.
$P < 0.05$ was considered statistically significant and $P = 0.05$–0.07 was considered marginally significant.
Quantitative variables were obtained from one-way ANOVA and presented as mean ± SD, and categorical variables were obtained from the Chi-Square test and presented as frequency and percentage.
Carbohydrate quality index includes total fiber, glycemic index, whole grains to total grains ratio, and solid carbohydrate to total carbohydrate ratio.
[a]Significant difference with Bonferroni analysis was seen between T1 and T3.
Bold values indicate significant and marginally significant *p*-values.

risk factors of participants across tertiles of the CQI, as shown in Table 4.

The association between CQI with CVD risk factors, anthropometric measures, and body composition of study participants

According to Table 5, in the crude model, SBP ($P = 0.02$) and DBP ($P = 0.04$) had an inverse significant association with CQI in the second tertile. Furthermore, DBP ($P = 0.04$), HOMA-IR ($P = 0.001$), WC ($P = 0.03$), BMI ($P = 0.03$), BFM ($P = 0.02$), BF ($P = 0.01$), FMI ($P = 0.02$), TF (kg) ($P = 0.04$), and TF (%) ($P = 0.02$) had an inverse significant association with CQI in third tertile. After adjusting for confounding variables, such as age, BMI, energy intake, and physical activity, SBP ($\beta = -6.10$; 95% CI $= -10.11, -2.10$; $P = 0.003$) and DBP ($\beta = -3.76$; 95% CI $= -6.63, -0.89$; $P = 0.01$) had an inverse significant association with CQI in the second tertile. Furthermore, DBP ($\beta = -3.11$; 95% CI $= -6.15, -0.08$; $P = 0.04$), HOMA-IR ($\beta = -0.53$; 95% CI $= -0.94, -0.12$; $P = 0.01$), WC ($\beta = -3.18$; 95% CI $= -6.26, -0.10$; $P = 0.04$), WHR ($\beta = -0.01$; 95% CI $= -0.03, -0.001$; $P = 0.03$), BFM ($\beta = -2.87$; 95% CI $= -5.48, -0.26$; $P = 0.03$), BF ($\beta = -2.06$; 95% CI $= -3.82, -0.30$; $P = 0.02$), FMI ($\beta = -1.07$;

TABLE 3 Dietary intake of study participants among tertiles of the CQI ($n = 291$).

Dietary intake	Tertiles of CQI			*P*-value*	*P*-value**
	T1 $n = 103$ Mean ± SD <10	T2 $n = 99$ Mean ± SD 10–13	T3 $n = 89$ Mean ± SD >13		
CQI components					
Fiber intake (gr/day)[a,b,c]	31.55 ± 8.71	42.26 ± 13.79	50.54 ± 13.43	**<0.001**	**<0.001**
Glycemic index[a,b,c]	59.61 ± 5.30	56.40 ± 5.82	53.82 ± 5.95	**<0.001**	**<0.001**
Solid CHO (g/day)/total CHO (g/day)[a,b,c]	0.59 ± 0.28	0.74 ± 0.13	0.81 ± 0.09	**<0.001**	**<0.001**
Whole grain (g/day)/ total grain (g/day)[b,c]	0.01 ± 0.01	0.02 ± 0.02	0.04 ± 0.04	**<0.001**	**<0.001**
Food group components					
Energy (Kcal/day)	2,601.05 ± 751.49	2,472.36 ± 805.38	2,783.37 ± 658.46	**0.01**	–
Fruits (g/day)[b]	457.51 ± 292.92	502.25 ± 326.31	641.16 ± 373.24	**<0.001**	**0.003**
Vegetables (g/day)[b,c]	347.97 ± 211.43	402.94 ± 261.79	566.71 ± 269.61	**<0.001**	**<0.001**
Nuts (g/day)[b]	13.08 ± 14.25	11.78 ± 11.38	18.72 ± 21.32	**0.008**	**0.06**
Legumes (g/day)[b,c]	38.41 ± 25.69	48.46 ± 36.48	73.91 ± 51.51	**<0.001**	**<0.001**
Dairy (g/day)	366.78 ± 245.37	355.98 ± 203.60	446.13 ± 280.98	**0.02**	0.19
Eggs (g/day)	19.64 ± 14.94	20.98 ± 12.56	24.82 ± 14.56	**0.03**	0.10
Fish and seafood (g/day)	10.46 ± 10.06	11.91 ± 12.70	11.94 ± 13.71	0.61	0.49
Red meat (g/day)	20.95 ± 16.74	21.17 ± 20.12	22.42 ± 18.78	0.84	0.72
Whole grains (g/day)[b,c]	3.76 ± 7.15	5.73 ± 9.51	14.07 ± 11.55	**<0.001**	**<0.001**
Refined grains (g/day)	437.70 ± 190.25	420.82 ± 234.69	438.96 ± 237.00	0.81	0.48
Total fiber (g/day)	35.43 ± 13.61	43.93 ± 18.53	57.55 ± 17.28	**<0.001**	**0.01**
Caffeine (g/day)	156.80 ± 105.56	159.85 ± 211.45	135.21 ± 111.61	0.48	0.24
Tea and coffee (g/day)	746.58 ± 519.84	781.56 ± 1057.51	687.49 ± 575.38	0.69	0.40
Macronutrients					
Protein (g/day)[a,b]	83.64 ± 26.88	85.40 ± 32.45	96.89 ± 23.45	**0.002**	**0.004**
Carbohydrate (g/day)[b,c]	358.79 ± 121.63	349.61 ± 122.27	411.70 ± 107.60	**0.001**	**<0.001**
Total fat (g/day)[b]	99.72 ± 34.58	89.39 ± 35.10	93.70 ± 28.85	0.08	**<0.001**
Fatty acid subtypes					
Saturated fatty acids (g/day)[b]	30.04 ± 10.99	26.12 ± 11.53	27.69 ± 10.47	**0.04**	**<0.001**
Cholesterol (g/day)	252.62 ± 105.68	244.20 ± 109.99	261.20 ± 97.82	0.54	0.82
MUFA (g/day)[b,c]	33.28 ± 12.91	30.13 ± 12.10	30.27 ± 9.93	0.10	**<0.001**
PUFA (g/day)[b]	21.16 ± 11.03	19.26 ± 8.53	19.65 ± 6.98	0.29	**0.06**
Linoleic acid (g/day)[b]	18.48 ± 10.43	16.66 ± 8.12	16.75 ± 6.62	0.24	**0.04**
Linolenic acid (g/day)	1.30 ± 0.79	1.09 ± 0.55	1.31 ± 0.62	**0.04**	0.22
EPA (g/day)	0.02 ± 0.03	0.03 ± 0.03	0.03 ± 0.04	0.42	0.47
DHA (g/day)	0.09 ± 0.10	0.10 ± 0.10	0.11 ± 0.13	0.51	0.54
Trans fatty acids (g/day)	0.000 ± 0.003	0.000 ± 0.001	0.001 ± 0.002	0.56	0.69
Micronutrients					
Sodium (mg/day)	4,226.48 ± 1,586.18	4,174.70 ± 1,460.59	4,321.61 ± 1,173.02	0.77	0.29
Potassium (mg/day)[a,b,c]	3,939.40 ± 1,505.00	4,080.78 ± 1,480.07	4,987.73 ± 1,475.67	**<0.001**	**<0.001**
Calcium (mg/day)[b,c]	1,077.20 ± 417.72	1,092.70 ± 368.99	1,325.94 ± 415.61	**<0.001**	**<0.001**
Phosphorus (mg/day)[a,b]	1,533.38 ± 507.09	1,562.34 ± 523.42	1,814.77 ± 471.73	**<0.001**	**<0.001**
Iron (mg/day)[a,b,c]	16.88 ± 5.48	17.89 ± 6.39	21.36 ± 4.90	**<0.001**	**<0.001**
Zinc (mg/day)[b]	12.32 ± 4.17	12.21 ± 4.33	14.18 ± 3.75	**0.001**	**0.007**

(Continued)

TABLE 3 (Continued)

Dietary intake	Tertiles of CQI			*P*-value*	*P*-value**
	T1 *n* = 103 Mean ± SD <10	T2 *n* = 99 Mean ± SD 10–13	T3 *n* = 89 Mean ± SD >13		
Selenium (μg/day)[a]	113.03 ± 41.36	118.05 ± 45.96	128.79 ± 38.48	**0.03**	**0.03**
Magnesium (mg/day)[a,b,c]	421.51 ± 143.40	433.00 ± 148.64	523.26 ± 128.15	**<0.001**	**<0.001**
Copper (mg/day)[a,b,c]	1.76 ± 0.59	1.92 ± 0.82	2.30 ± 0.57	**<0.001**	**<0.001**
Manganese (mg/day)	6.67 ± 2.45	6.91 ± 3.35	7.62 ± 2.44	**0.05**	0.17
Chromium (mg/day)	0.10 ± 0.08	0.10 ± 0.08	0.12 ± 0.08	0.22	0.48
Vitamin A (IU/day)[b,c]	694.11 ± 388.69	710.08 ± 378.48	924.52 ± 420.04	**<0.001**	**0.001**
Vitamin D (μg/day)	1.73 ± 1.67	1.90 ± 1.52	2.25 ± 1.60	0.08	0.23
Vitamin E (mg/day)[c]	17.64 ± 9.54	17.82 ± 10.48	16.31 ± 7.38	0.48	**0.06**
Vitamin K (μg/day)[b,c]	164.56 ± 107.08	194.32 ± 159.80	284.28 ± 265.64	**<0.001**	**<0.001**
Vitamin C (mg/day)[b]	171.90 ± 105.43	191.20 ± 149.65	225.51 ± 111.86	**0.01**	**0.03**
Vitamin B1 (mg/day)[a,b]	1.96 ± 0.61	2.01 ± 0.69	2.29 ± 0.59	**0.001**	**<0.001**
Vitamin B2 (mg/day)[a,b]	2.00 ± 0.77	2.16 ± 0.89	2.42 ± 0.69	**0.001**	**<0.001**
Vitamin B3 (mg/day)[a,b]	23.46 ± 7.94	25.08 ± 11.76	27.31 ± 6.32	**0.01**	**0.003**
Pantothenic acid (mg/day)[b]	6.04 ± 2.02	6.25 ± 2.84	7.17 ± 2.02	**0.002**	**0.01**
Vitamin B6 (mg/day)[b]	2.02 ± 0.67	2.05 ± 0.76	2.42 ± 0.59	**<0.001**	**<0.001**
Vitamin B8 (mg/day)[a,b]	33.64 ± 14.00	37.47 ± 20.42	44.09 ± 13.42	**<0.001**	**<0.001**
Vitamin B9 (μg/day)[a,b,c]	558.34 ± 163.88	585.67 ± 177.49	679.13 ± 163.60	**<0.001**	**<0.001**
Vitamin B12 (μg/day)	4.36 ± 2.35	4.25 ± 2.53	4.36 ± 2.30	0.93	0.43

(–), not calculated; CHO, carbohydrates; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acids; N, number; PUFA, polyunsaturated fatty acids; SD, standard deviation; T, tertile.

*The *P*-values were obtained by the use of ANOVA.

**The *P*-values were obtained by the use of ANCOVA after adjustment for energy intake.

$P < 0.05$ was considered statistically significant and $P = 0.05$–0.07 was considered marginally significant.

Quantitative variables were obtained from one-way ANOVA and presented as mean ± SD.

Carbohydrate quality index includes total fiber, glycemic index, whole grains to total grains ratio, and solid carbohydrate to total carbohydrate ratio.

[a]Significant difference with Bonferroni analysis was seen between T1 and T2.

[b]Significant difference with Bonferroni analysis was seen between T1 and T3.

[c]Significant difference with Bonferroni analysis was seen between T2 and T3.

Bold values indicate significant and marginally significant *p*-values.

95% CI = −2.09, −0.04; $P = 0.04$), TF (kg) (β = −1.14; 95% CI = −2.28, −0.003; $P = 0.04$), and TF (%) (β = −22.98; 95% CI = −44.38, −1.57; $P = 0.03$) had an inverse significant association and BMI (β = −1.21; 95% CI = −2.50, 0.07; $P = 0.06$) had an inverse marginally significant association with CQI in the third tertile compare to T1. Based on this table, in crude model, more adherence to a higher CQI diet compare to lower adherence, was negatively significantly associated DBP (*P* for trend = 0.03), HOMA-IR (*P* for trend = 0.001), WC (*P* for trend = 0.03), BMI (*P* for trend = 0.03), BFM (*P* for trend = 0.02), BF (*P* for trend = 0.01), FMI (*P* for trend = 0.02), TF (kg) (*P* for trend = 0.04), and TF (%) (*P* for trend = 0.03). After adjusting for confounders, in model 1, greater adherence to a diet with high CQI was positively and significantly associated with a DBP (*P* for trend = 0.04), and negatively with HOMA-IR (*P* for trend = 0.01), WC (*P* for trend = 0.04), WHR (*P* for trend = 0.03), BFM (*P* for trend = 0.03), BF (*P* for trend = 0.02), FMI (*P* for trend = 0.04), and TF (%) (*P* for trend = 0.03), compare to reference group. Also, after adjusting for confounders, greater adherence to a higher CQI diet was positively and marginally significantly associated with SBP (*P* for trend = 0.05), and negatively with BMI (*P* for trend = 0.06) and TF (kg) (*P* for trend = 0.05).

Discussion

To the best of our knowledge, the current study is the first study to investigate the association between CQI with CVD risk factors in Iranian women with obesity and overweight. The present study revealed after adjusting for age, BMI, energy intake, and physical activity, the consumption of a diet with high CQI was inversely related to blood pressure, insulin resistance, anthropometric measures, including WC, WHR, and BMI, and body composition, such as BF.

TABLE 4 CVD risk factors, anthropometric measures, and body composition of study participants among tertiles of the CQI ($n = 291$).

CVD risk factors	Models	Tertiles of CQI			*P*-value*	*P*-value**
		T1 $n = 103$ Mean ± SD <10	T2 $n = 99$ Mean ± SD 10–13	T3 $n = 89$ Mean ± SD >13		
Blood pressure						
SBP (mmHg)	Crude	113.87 ± 12.90[1]	109.32 ± 13.58	111.63 ± 14.59	0.07	0.15
	Model 1	113.87 ± 1.29[2]	109.32 ± 1.40	111.63 ± 1.56		
DBP (mmHg)	Crude	79.60 ± 9.65	76.78 ± 9.29	76.74 ± 9.72	**0.06**	0.09
	Model 1	79.60 ± 0.97	76.78 ± 0.95	76.74 ± 1.04		
Blood parameters						
FBS (mg/dl)	Crude	87.57 ± 10.58	88.56 ± 9.93	86.26 ± 8.05	0.31	0.46
	Model 1	87.57 ± 1.14	88.56 ± 1.09	86.26 ± 0.91		
TC (mg/dl)	Crude	183.96 ± 35.08	188.42 ± 40.78	182.96 ± 32.39	0.59	0.93
	Model 1	183.96 ± 3.80	188.42 ± 4.47	182.96 ± 3.66		
TG (mg/dl)	Crude	115.27 ± 57.53	124.52 ± 63.67	114.97 ± 58.14	0.51	0.52
	Model 1	115.27 ± 6.24	124.52 ± 7.03	114.97 ± 6.66		
HDL (mg/dl)	Crude	46.44 ± 9.20	46.50 ± 11.99	47.52 ± 11.32	0.78	0.79
	Model 1	46.44 ± 0.99	46.50 ± 1.31	47.52 ± 1.28		
LDL (mg/dl)	Crude	95.60 ± 22.23	94.18 ± 26.93	95.32 ± 23.44	0.92	0.45
	Model 1	95.60 ± 2.41	94.18 ± 2.95	95.32 ± 2.65		
hs-CRP (mg/L)	Crude	4.94 ± 4.91	3.89 ± 4.57	4.12 ± 4.44	0.32	0.66
	Model 1	4.94 ± 0.55	3.89 ± 0.50	4.12 ± 0.51		
Anthropometric parameters						
NC (cm)	Crude	37.12 ± 2.61	37.37 ± 3.93	38.22 ± 12.08	0.65	0.60
	Model 1	37.12 ± 0.30	37.37 ± 0.48	38.22 ± 1.46		
WC (cm)[b]	Crude	100.26 ± 10.99	99.14 ± 9.94	97.26 ± 8.78	0.11	**0.02**
	Model 1	100.26 ± 1.08	99.14 ± 1.00	97.26 ± 0.93		
WHR[b]	Crude	0.93 ± 0.05	1.86 ± 9.19	0.92 ± 0.05	0.37	**0.007**
	Model 1	0.93 ± 0.00	1.86 ± 0.92	0.92 ± 0.005		
BMI (kg/m^2)[b]	Crude	31.62 ± 4.96	31.15 ± 4.34	30.28 ± 3.33	0.09	**0.06**
	Model 1	31.62 ± 0.48	31.15 ± 0.43	30.28 ± 0.35		
Body composition						
BFM (kg)[b]	Crude	35.19 ± 9.91	34.32 ± 8.55	32.30 ± 6.91	**0.06**	**0.02**
	Model 1	35.19 ± 0.97	34.32 ± 0.86	32.30 ± 0.73		
FFM (kg)	Crude	47.23 ± 5.74	46.13 ± 5.38	46.97 ± 5.59	0.35	0.87
	Model 1	47.23 ± 0.56	46.13 ± 0.54	46.97 ± 0.59		
BF (%)[b]	Crude	42.06 ± 5.40	42.19 ± 5.24	40.13 ± 5.80	**0.01**	**0.01**
	Model 1	42.06 ± 0.53	42.19 ± 0.52	40.13 ± 0.61		
VFA (cm^2)	Crude	165.94 ± 43.04	182.00 ± 171.14	155.88 ± 35.87	0.22	0.14
	Model 1	165.94 ± 4.24	182.00 ± 17.28	155.88 ± 3.80		
VFL (cm)	Crude	17.68 ± 19.34	15.70 ± 3.31	16.55 ± 14.59	0.61	0.74
	Model 1	17.68 ± 1.91	15.70 ± 0.33	16.55 ± 1.54		
FFMI	Crude	18.07 ± 1.61	17.82 ± 1.47	19.42 ± 13.90	0.33	0.99
	Model 1	18.07 ± 0.15	17.82 ± 0.14	19.42 ± 1.48		
FMI[b]	Crude	13.53 ± 3.73	13.41 ± 3.46	12.43 ± 2.76	**0.05**	**0.01**
	Model 1	13.53 ± 0.36	13.41 ±.034	12.43 ± 0.29		

(Continued)

TABLE 4 (Continued)

CVD risk factors	Models	Tertiles of CQI			*P*-value*	*P*-value**
		T1 *n* = 103 Mean ± SD <10	T2 *n* = 99 Mean ± SD 10–13	T3 *n* = 89 Mean ± SD >13		
TF (kg)[b]	Crude	17.01 ± 3.97	16.66 ± 3.62	15.94 ± 3.42	0.12	**0.01**
	Model 1	17.01 ± 0.39	16.66 ± 0.36	15.94 ± 0.36		
TF (%)[b]	Crude	322.09 ± 73.76	317.46 ± 72.24	299.98 ± 61.26	0.07	**0.009**
	Model 1	322.09 ± 7.26	317.46 ± 7.29	299.98 ± 6.49		
HOMA-IR index[a]	Crude	3.66 ± 1.50	3.38 ± 1.23	2.97 ± 0.97	**0.003**	**0.007**
	Model 1	3.66 ± 0.16	3.38 ± 0.14	2.97 ± 0.11		

BF, body fat percentage; BFM, body fat mass; BMI, body mass index; CQI, carbohydrate quality index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FFM, fat-free mass; FFMI, fat-free mass index; FMI, fat mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NC, neck circumference; SBP, systolic blood pressure; T, tertile; TC, total cholesterol; TF, trunk fat; TG, triglyceride; VFA, visceral fat area; VFL, visceral fat level; WC, waist circumference; WHR, waist-hip ratio.

Participants were divided into categories called tertiles.

*The *P*-values were obtained by the use of ANOVA.

**The *P*-values were obtained by the use of ANCOVA after adjustment for age, BMI, energy intake, and physical activity (MET minutes/week). BMI is considered a collinear variable for anthropometric ad body composition measurements.

$P < 0.05$ was considered statistically significant and $P = 0.05$–0.07 was considered marginally significant.

[1]Unadjusted, mean ± SD.

[2]Adjusted for Carbohydrate quality index includes total fiber, glycemic index, whole grains to total grains ratio, and solid carbohydrate to total carbohydrate ratio.

[a]Significant difference with Bonferroni analysis was seen between T1 and T3.

[b]Significant difference with Bonferroni analysis was seen between T2 and T3.

Bold values indicate significant and marginally significant *p*-values.

The results of a previous study showed a consistently inverse relationship between the CQI with the incidence of CVD. Indeed, these results emphasized that, in terms of the association between each of the CQI components with CVD, there was only a significant relationship between the whole grains/total grains ratio with CVD (33). Another study revealed an inverse association between CQI and CVD risk factors including HbA1c, FBS, TG, SBP, DBP, TC, and HDL (55). Fiber intake, as one of the CQI components, affects hypertension, metabolic syndrome components, insulin resistance, and LDL (54, 56–59). It also affects inflammatory markers such as hs-CRP (54, 56). GI, another CQI component, was shown to increase postprandial glucose, insulin responses, TG, and non-HDL cholesterol, and decrease HDL cholesterol (60, 61). Whole grains are one of the CQI components that in previous studies was shown to have significant effects on HDL, LDL, TC, HbA1c, and CRP (62). In the present study, an inverse significant association between SBP, DBP, and HOMA-IR with consumption of a high CQI diet was seen. Also, concordant with previous studies, an inverse relationship was seen between consumption of a diet with high CQI with LDL and hs-CRP, although their relationships were not significant ($P > 0.05$), which may be due to the small sample size. Even though the reduction in TC and FBS was observed with greater increases in CQI in previous studies (55), there was no association was seen between CQI with TC and FBS in our study. The small sample size may have contributed to this, therefore more studies with larger samples are needed.

In terms of anthropometric measures, some evidence has indicated a relationship between CQI with body weight and WC (55). A population-based study suggested an inverse association between CQI with abdominal obesity in men (23). Indeed, in previous studies, fiber intake was associated with obesity, WHR, WC, body weight, and BMI (54, 56, 63–65). Also, an association was seen between GI with body weight and obesity (66). In previous studies, an inverse association was seen between whole grains with central obesity and WC (67, 68). In addition, the results of a cohort study suggested a positive association between liquid carbohydrates with body weight (69). Concordant with these results, we concluded that there is a relationship between CQI with WHR, WC, and BMI. However, our results showed no significant association between CQI with body weight and abdominal or general obesity.

It has been revealed that an association exists between dietary fiber intake with skeletal muscle mass, BFM, and muscle-to-fat ratio (MFR) among women with type 2 diabetes (70), although one study showed no association (71). It has been asserted that diets rich in fiber can elicit weight-loss and BF loss compared to a diet high in refined grains (24). Also, low GI diet has been reported to cause BFM loss (26). In this study, we observed a strong relationship between consumption of a high CQI diet with body composition including BFM, BF, FMI, and TF.

Some possible mechanisms have been suggested pertaining to the association between CQI with CVD risk factors. Foods

TABLE 5 The association between CQI with CVD risk factors, anthropometric measures, and body composition of study participants ($n = 291$).

CVD risk factors	Models	Tertiles	β ± SE	95% CI	*P*-value*	*P* trend
Blood pressure						
SBP (mmHg)	Crude	T2	−4.54 ± 1.95	−8.38, −0.71	**0.02**	0.23
		T3	−2.24 ± 1.99	−6.16, 1.67	0.26	
	Model 1	T2	−6.10 ± 2.04	−10.11, −2.10	**0.003**	**0.05**
		T3	−3.47 ± 2.15	−7.70, 0.75	0.10	
DBP (mmHg)	Crude	T2	−2.81 ± 1.36	−5.50, −0.13	**0.04**	**0.03**
		T3	−2.85 ± 1.39	−5.59, −0.12	**0.04**	
	Model 1	T2	−3.76 ± 1.46	−6.63, −0.89	**0.01**	**0.04**
		T3	−3.11 ± 1.54	−6.15, −0.08	**0.04**	
Blood parameters						
FBS (mg/dl)	Crude	T2	0.99 ± 1.47	−1.90, 3.88	0.50	0.40
		T3	−1.30 ± 1.49	−4.24, 1.63	0.38	
	Model 1	T2	1.07 ± 1.54	−1.94, 4.09	0.48	0.18
		T3	−2.14 ± 1.58	−5.25, 0.97	0.07	
TC (mg/dl)	Crude	T2	4.45 ± 5.57	−6.46, 15.37	0.42	0.88
		T3	−1.00 ± 5.66	−12.09, 10.09	0.85	
	Model 1	T2	5.50 ± 5.80	−5.87, 16.88	0.34	0.79
		T3	−1.58 ± 5.98	−13.30, 10.14	0.79	
TG (mg/dl)	Crude	T2	9.25 ± 9.20	−8.79, 27.30	0.31	0.99
		T3	−0.29 ± 9.39	−18.70, 18.11	0.97	
	Model 1	T2	16.15 ± 9.99	−3.43, 35.74	0.10	0.34
		T3	9.57 ± 10.34	−10.70, 29.86	0.35	
HDL (mg/dl)	Crude	T2	0.05 ± 1.66	−3.21, 3.33	0.97	0.53
		T3	1.07 ± 1.69	−2.24, 4.40	0.52	
	Model 1	T2	−0.71 ± 1.86	−4.36, 2.93	0.70	0.78
		T3	−0.52 ± 1.91	−4.28, 3.23	0.78	
LDL (mg/dl)	Crude	T2	−1.41 ± 3.72	−8.72, 5.88	0.70	0.93
		T3	−0.27 ± 3.78	−7.69, 7.13	0.94	
	Model 1	T2	−0.57 ± 3.98	−8.38, 7.22	0.88	0.85
		T3	−0.75 ± 4.10	−8.80, 7.28	0.85	
hs-CRP (mg/L)	Crude	T2	−1.05 ± 0.73	−2.48, 0.37	0.14	0.26
		T3	−0.82 ± 0.74	−2.28, 0.63	0.27	
	Model 1	T2	−0.13 ± 0.78	−1.67, 1.40	0.86	0.87
		T3	−0.13 ± 0.80	−1.70, 1.44	0.87	
Anthropometric parameters						
NC (cm)	Crude	T2	0.24 ± 1.24	−2.18, 2.68	0.84	0.37
		T3	1.10 ± 1.23	−1.31, 3.52	0.37	
	Model 1	T2	0.23 ± 1.47	−2.66, 3.12	0.87	0.38
		T3	1.28 ± 1.47	−1.61, 4.190	0.38	
WC (cm)	Crude	T2	−1.11 ± 1.40	−3.86, 1.63	0.42	**0.03**
		T3	−3.00 ± 1.44	−5.82, −0.17	**0.03**	
	Model 1	T2	−0.47 ± 1.50	−3.41, 2.46	0.75	**0.04**
		T3	−3.18 ± 1.57	−6.26, −0.10	**0.04**	
WHR	Crude	T2	0.92 ± 0.75	−0.54, 2.39	0.21	0.96
		T3	−0.01 ± 0.77	−1.52, 1.49	0.98	

(Continued)

TABLE 5 (Continued)

CVD risk factors	Models	Tertiles	β ± SE	95% CI	*P*-value*	*P* trend
	Model 1	T2	−0.001 ± 0.007	−0.01, 0.01	0.85	**0.03**
		T3	−0.01 ± 0.008	−0.03, −0.001	**0.03**	
BMI (kg/m^2)	Crude	T2	−0.46 ± 0.60	−1.65, 0.71	0.43	**0.03**
		T3	−1.33 ± 0.62	−2.55, −0.12	**0.03**	
	Model 1	T2	−0.21 ± 0.62	−1.44, 1.01	0.73	**0.06**
		T3	−1.21 ± 0.65	−2.50, 0.07	**0.06**	
Body composition						
BFM (kg)	Crude	T2	−0.87 ± 1.21	−3.24, 1.49	0.46	**0.02**
		T3	−2.89 ± 1.24	−5.32, −0.46	**0.02**	
	Model 1	T2	−0.10 ± 1.27	−2.59, 2.38	0.93	**0.03**
		T3	−2.87 ± 1.33	−5.48, −0.26	**0.03**	
FFM (kg)	Crude	T2	−1.09 ± 0.78	−2.63, 0.43	0.16	0.70
		T3	−0.25 ± 0.80	−1.83, 1.31	0.75	
	Model 1	T2	−0.84 ± 0.87	−2.56, 0.87	0.33	0.92
		T3	0.09 ± 0.91	−1.70, 1.89	0.92	
BF (%)	Crude	T2	0.12 ± 0.76	−1.38, 1.63	0.87	**0.01**
		T3	−1.93 ± 0.78	−3.47, −0.38	**0.01**	
	Model 1	T2	0.53 ± 0.85	−1.15, 2.21	0.53	**0.02**
		T3	−2.06 ± 0.89	−3.82, −0.30	**0.02**	
VFA (cm^2)	Crude	T2	16.06 ± 14.69	−12.73, 44.85	0.27	0.55
		T3	−10.06 ± 15.06	−39.59, 19.46	0.50	
	Model 1	T2	21.77 ± 18.30	−14.09, 57.63	0.23	0.53
		T3	−12.37 ± 19.15	−49.91, 25.16	0.51	
VFL (cm)	Crude	T2	−1.97 ± 1.99	−5.89, 1.93	0.32	0.56
		T3	−1.13 ± 2.04	−5.14, 2.88	0.58	
	Model 1	T2	−2.51 ± 2.53	−7.47, 2.45	0.32	0.51
		T3	−1.71 ± 2.64	−6.90, 3.48	0.51	
FFMI	Crude	T2	−0.24 ± 1.09	−2.38, 1.89	0.82	0.25
		T3	1.34 ± 1.12	−0.86, 3.54	0.23	
	Model 1	T2	−0.33 ± 1.35	−2.99, 2.33	0.80	0.28
		T3	1.54 ± 1.42	−1.24, 4.33	0.27	
FMI	Crude	T2	−0.12 ± 0.47	−1.04, 0.80	0.80	**0.02**
		T3	−1.10 ± 0.48	−2.05, −0.14	**0.02**	
	Model 1	T2	0.12 ± 0.49	−0.85, 1.09	0.81	**0.04**
		T3	−1.07 ± 0.52	−2.09, −0.04	**0.04**	
TF (kg)	Crude	T2	−0.34 ± 0.51	−1.36, 0.67	0.50	**0.04**
		T3	−1.07 ± 0.53	−2.11, −0.03	**0.04**	
	Model 1	T2	−0.11 ± 0.55	−1.20, 0.98	0.84	**0.05**
		T3	−1.14 ± 0.58	−2.28, −0.003	**0.04**	
TF (%)	Crude	T2	−4.63 ± 9.77	−23.78, 14.52	0.63	**0.03**
		T3	−22.10 ± 10.02	−41.75, −2.45	**0.02**	
	Model 1	T2	−1.29 ± 10.43	−21.74, 19.16	0.90	**0.03**
		T3	−22.98 ± 10.92	−44.38, −1.57	**0.03**	

(Continued)

TABLE 5 (Continued)

CVD risk factors	Models	Tertiles	β ± SE	95% CI	*P*-value*	*P* trend
HOMA-IR index	Crude	T2	−0.28 ± 0.19	−0.67, 0.10	0.15	**0.001**
		T3	−0.69 ± 0.20	−1.08, −0.29	**0.001**	
	Model 1	T2	−0.20 ± 0.20	−0.61, 0.19	0.31	**0.01**
		T3	−0.53 ± 0.21	−0.94, −0.12	**0.01**	

BF, body fat percentage; BFM, body fat mass; BMI, body mass index; CQI, carbohydrate quality index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FFM, fat-free mass; FFMI, fat-free mass index; FMI, fat mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NC, neck circumference; SBP, systolic blood pressure; TC, total cholesterol; TF, trunk fat; TG, triglyceride; VFA, visceral fat area; VFL, visceral fat level; WC, waist circumference; WHR, waist-hip ratio.

β and CI were obtained from linear regression and T1 is considered a reference group.

Participants were divided into categories called tertiles.

*The *P*-values were obtained by the use of linear regression after adjustment for age, BMI, energy intake, and physical activity.

$P < 0.05$ was considered statistically significant and $P = 0.05$–0.07 was considered marginally significant.

Carbohydrate quality index includes total fiber, glycemic index, whole grains to total grains ratio, and solid carbohydrate to total carbohydrate ratio.

Bold values indicate significant and marginally significant *p*-values.

reach in fiber take more time to chew and so affect hunger reduction, increasing satiety, glucose control, improving insulin sensitivity, lipid absorption, lipid and carbohydrate oxidation regulation, and slowing down intestinal transit, that can cause body weight regulation (38, 39, 72, 73). Furthermore, fiber can fermentate in the colon by microflora and produce short-chain fatty acids (SCFAs), which contribute to improving health (74). Although the role of soluble and insoluble fiber is different, both are involved in reducing CVD risk factors and healthy body composition. Indeed, soluble fiber, due to its higher viscosity, induces satiety and controls hypercholesterolemia, and insoluble fiber, through inducing more satiety, and decreasing weight and WC, plays an important role (75–77). The mechanism by which dietary fiber lowers blood pressure levels remains unclear (78). Fermentation of dietary fiber in the intestine produces SCFAs. It has been seen that these SCFAs can lower blood pressure. The important mechanism through which SCFAs affect blood pressure is that SCFAs activate G protein-coupled receptors 43 and olfactory receptor 78 expressed in the kidney. This process inhibits the release of renin, which contributes to the regulation of blood pressure (79–81). Moreover, a high GI diet leads to insulin resistance, oxidative stress, and inflammation that aggravates dyslipidemia (82, 83). A high GI diet reduces fat oxidation and increases carbohydrate oxidation causing high-fat storage (84). On the other hand, a low GI diet leads to greater satiety and decreased desire for food intake, affecting energy intake and body composition balance (37). A high GI diet through increased postprandial insulin, causes activation of the sympathetic nervous system, sodium retention, and increased blood volume, resulting in increased blood pressure (85). Whole grains, as compared to refined grains, cause slower digestion and absorption of starch, and thus reduce insulin response and blood glucose. Also, whole grains induce greater satiety and reduce appetite leading to lower energy consumption and obesity prevention or improvement (38, 45). In addition, whole grains have been suggested to dilate blood vessels through the activity of endothelial nitric oxide, increase nitric oxide bioavailability, decrease inflammation, have antioxidant effects, increase arterial baroreceptor reflex function, and gut microbiota changes (86–89). So thus, decreasing blood pressure. Liquid carbohydrates, due to higher GI, increasing the risk of obesity (90); in addition, they can induce appetite, increase postprandial glucose and decrease insulin sensitivity compared to solid carbohydrates (43, 91).

The present study has several strengths. Based on our knowledge, this is the first study investigating the relationship between CQI with CVD risk factors. Also, we conducted this study on obese and overweight Iranian women, allowing detailed insight into this population. Despite these strengths, the study was not without some limitations. First, the sample size was relatively small and was performed only on women. Second, due to the cross-sectional design of the study, the findings do not establish causality between CQI with CVD risk factors. Third, we used the FFQ for obtaining the usual dietary intake which is based on participants' memory, thus may have resulted in recall bias. Forth, some measurement errors may have occurred while measuring.

Conclusion

Consistent with previous studies, we found that consumption of a high CQI diet was negatively associated with blood pressure, insulin resistance (HOMA-IR), anthropometric measures, including WC, WHR, BMI, and body composition, such as BF. Clearly, further studies are warranted to confirm the veracity of these results.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Tehran University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

This project was designed and implemented by DK, AM, and KM. Data were analyzed and interpreted by FS. The manuscript was created by DK, CC, and AM. KM and AM supervised the overall project. This manuscript was revised by CC and ED. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Phase angle derived from bioelectrical impedance analysis as a marker for predicting sarcopenia

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Sarcopenia is commonly defined as the age-related loss of muscle mass and function and may be caused by several factors, such as genetics, environmental conditions, lifestyle, drug use, and, in particular, comorbidities. People with pre-existing conditions are more likely to develop sarcopenia and subsequently have a less favorable prognosis. Recently, phase angle (PhA), which is derived from bioelectrical impedance analysis (BIA), has received a great deal of attention, and numerous studies have been carried out to examine the relationship between PhA and sarcopenia in different conditions. Based on these studies, we expect that PhA could be used as a potential marker for sarcopenia in the future.

KEYWORDS

bioimpedance analysis, muscle mass, muscle strength, phase angle, sarcopenia, survival

Introduction

Sarcopenia is a skeletal muscle disorder characterized by the accumulated loss of muscle mass and strength, and starts to develop at around 40 years of age for most sufferers (1). A recent epidemiological study found that the prevalence of sarcopenia varies between 10 and 27% across the world (2). Currently, an increasing number of studies have shown that community-dwelling people suffering from severe sarcopenia have an increased risk of adverse outcomes, such as falls, fractures (3), mobility disorders, lower quality of life, and even death (4). In addition, patients with sarcopenia have longer hospital stays and worse progression-free survival (PFS) and overall survival (OS) (5–7). In general, there are two diagnostic criteria for sarcopenia that are widely used: one is the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), which uses computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy x-ray absorptiometry (DXA) to diagnose sarcopenia (8), and the other is the 2019 Asian Working Group for Sarcopenia (AWGS), which uses dual-energy X-ray imaging (DXA) measurement of the appendicular skeletal muscle mass, low muscle strength (e.g., handgrip strength [HGS]), and low physical performance (e.g., walking speed) (9). Nonetheless, these complex procedures have some limitations, as they are unrepeatable

and always require professional guidance. Given this, a simple, cost-effective, reliable, and reproducible biomarker is urgently needed to screen for and predict sarcopenia.

Recently, there has been growing interest in bioelectrical impedance analysis (BIA), which is a safe, non-invasive, and inexpensive bedside method for assessing body composition (10). The operating principle uses the empirical regression equation to measure resistance, which is mainly determined by the intracellular and extracellular fluid, and reactance, which is produced by the double layer of the cell membranes (11, 12). However, the universal indicators associated with BIA, which include fat-free mass (FFM) and total body water (TBW), are frequently hampered by the patients' hydration status and distribution of intracellular and extracellular water when assessing body composition in different clinical situations (12).

Phase angle (PhA), another raw parameter of BIA, is calculated from the original data resistive resistance (R) and capacitive reactance (Xc) by the formula arctangent (Xc/R) × 180°/π at a frequency of 50 kHz (Figure 1), and this measure is less affected by body fluid distribution (10, 12, 13). Previous studies have shown that PhA is positively correlated with cell membrane integrity and cell function. When the cell membranes are intact and the cell functions are complete PhA increases, but the situation is the opposite when the cell membranes are damaged and the selective filtration function is reduced (13–16). In healthy people, PhA has been shown to be associated with age, gender, BMI, life factors, and race (17, 18). Presently, PhA is used to predict clinical outcomes and mortality for several diseases (5, 19, 20). In addition, an increasing number of studies have considered it to be an important tool for assessing nutrition (21, 22), and it has been proposed as a possible marker for diagnosing sarcopenia, according to the 2019 EWGSOP (8). However, the validity of this parameter as a marker for predicting sarcopenia has not been evaluated.

Therefore, this review aims to summarize the role of PhA as a predictive marker for sarcopenia and explore its utility under different conditions.

PhA prediction for sarcopenia in patients with cancer

Following extensive studies that compared patients with cancer to those without it, the former have been found to have a higher risk of developing cachexia, which can easily result in malnutrition and muscle loss, and lead to sarcopenia (6, 23). Based on the EWGSOP diagnosis criteria for sarcopenia, many studies have proved that a low PhA predicts sarcopenia risk in patients with colorectal cancer (24), gastric cancer (25), and prostate cancer (26). A cross-sectional study conducted with 124 patients in total with solid or hematologic cancer found that a low PhA is highly correlated with a high risk of sarcopenia [odds ratio (OR) = 1.74; 95% confidence interval (CI), 1.03–2.93; $P < 0.035$], after adjusting for hydration (27). A systematic review by Ji et al. involving 445 patients who were aged 65 years or older and with non-small cell lung cancer and digestive tract cancer

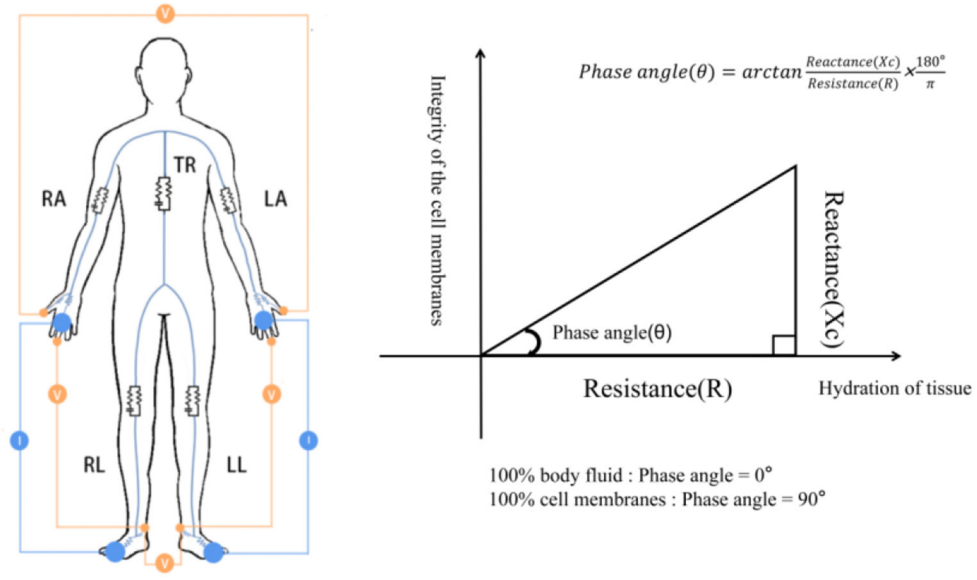

FIGURE 1
Diagram showing how PhA is measured. RA, right arm; LA, left arm; TR, trunk; RL, right leg; LL, left leg. The resistance and reactance to the voltage generated by the device is measured.

showed that PhA was related to sarcopenia (OR = 0.309; $P < 0.001$), with a cutoff point of 4.25° (28).

In addition to the cancer types above, for which the relationship between PhA and sarcopenia has been demonstrated, there are a large number of cancers for which this relationship has not been clearly shown as the associated studies only investigated whether PhA could predict nutritional status. A systematic review, which included 16 studies of patients with breast cancer, proved that PhA can serve as a predictor of nutritional and functional status but not sarcopenia, and the predominant reason for this was that breast cancer patients were less likely to suffer from sarcopenia, resulting in an ambiguous link between PhA and sarcopenia (29). Furthermore, in patients with hepatobiliary-pancreatic (HBP) cancer (30), head and neck cancer (31), ovarian cancer (32), esophageal cancer (33), and cervical cancer (34), PhA has only been associated with malnutrition, and, to date, no studies have investigated the relationship between PhA and sarcopenia. As such, although PhA may have potential as a new prediction marker for sarcopenia in patients with cancer, further studies are needed to confirm this.

PhA prediction for sarcopenia in patients with non-cancer diseases

Currently, a large number of studies have been carried out to evaluate whether PhA can be used a marker for predicting sarcopenia in patients with non-cancer diseases. For patients with cardiovascular diseases (CVDs), a retrospective cross-sectional analysis by Suguru Hirose et al. illustrated that PhA appears to be a useful marker for sarcopenia, and the cutoff value was 4.55° and 4.25° for males and females, respectively (35). Another study involving 310 patients with CVD found that PhA could be used to evaluate skeletal muscle damage caused by arteriosclerosis; however, only four of the patients had sarcopenia, so a relationship between PhA and sarcopenia could not be proven (36). For patients who underwent cardiovascular surgery, a significant correlation of PhA with sarcopenia was observed, demonstrating that PhA is probably a comprehensive indicator of sarcopenia (37). Overall, PhA may have a good predictive value for sarcopenia in patients with cardiac diseases.

A negative correlation between PhA and sarcopenia was observed in acute stroke patients and patients recovering from stroke; the cutoff points for sarcopenia in these instances were 5.28° for males and 4.62° for females (38), and 4.76° for males and 4.11° for females (39), respectively. A recent case series study involving 77 individuals demonstrated that for Parkinson's disease patients with sarcopenia, after adjusting for bias, only age (OR = 0.423; $P < 0.001$) was associated with PhA, but skeletal muscle mass index, grip strength, and gait speed, which were the diagnostic standards for sarcopenia, were not (40). Altogether, studies have not yet consistently shown that PhA can predict sarcopenia in patients with brain disease, and further research is needed to verify its predictive value in this context.

Meanwhile, a multicenter randomized trial involving 149 participants with chronic kidney disease (CKD) found that PhA could predict the presence of sarcopenia ($P = 0.001$) (41). A Poisson multivariate model put forward by de Amorin et al. (42), which included PhA, IL-6, and creatinine, was able to consistently predict sarcopenia in the patients with non-dialysis chronic kidney disease (ND-CKD). However, different results were obtained with kidney transplant patients. Kosoku et al. (43) found that PhA was negatively correlated with sarcopenia in kidney transplant patients, and the cutoff for predicting sarcopenia was 4.46°. A cross-sectional study involving 129 kidney transplant patients found that PhA was associated with HGS in renal transplant patients, but not sarcopenia (OR = 1.95; 95% CI: 0.71–5.39) (44). Another cross-sectional study, this time involving 346 patients who underwent maintenance hemodialysis in mainland China, found that PhA may have an optimistic predictive value for identifying sarcopenia (45). In kidney diseases, the difference is mainly concentrated in kidney transplant patients. Therefore, further research is needed to determine whether PhA can predict sarcopenia.

A study by Astrid Ruiz-Margáin, involving 413 cirrhosis patients with or without ascites, showed that PhA is lower in patients with chronic hepatitis than in patients without cirrhosis, with a cutoff value of 5.6° and 5.4° for males and females, respectively (46). Previous studies of patients with chronic obstructive pulmonary disease (COPD) (47) and peritoneal dialysis (PD) (48) have also showed that lower PhA can predict high sarcopenia risk.

Altogether, the studies above show that PhA is not a viable marker for sarcopenia in some diseases.

PhA prediction for sarcopenia in community-dwelling people

Contemporarily, the prospect of PhA as a marker of sarcopenia risk has gained considerable popularity in community-dwelling people. Investigative research of the elderly in Japan and Poland has shown that the early risk of sarcopenia is closely related to PhA, and the optimal cutoff point for distinguishing sarcopenia from those without sarcopenia was 4.05° for males and 3.55° for females (49), and 5.42° for males and 4.76° for females (50), respectively. A study by Basile et al. (51) involving 1,567 elderly people in Italy with an average age of 76.2 (±6.7) years found that males and females with sarcopenia had a lower PhA, which was positively correlated with a reduction of muscle mass (OR = 0.623, $P < 0.01$). Two studies on elderly Mexican people also found a predictive value of PhA for sarcopenia (52, 53).

Nevertheless, a cross-sectional study performed with 94 physically active older females drew different conclusions,

TABLE 1 Results of the studies with patients with different pathologies.

Disease	Direction of association between PhA and sarcopenia	Cutoff		AUROC	Sensitivity		Specificity		Diagnostic criteria	Location	Sample
		Male	Female		Male	Female	Male	Female			
Cancer											
Colorectal cancer (24)	Negative								EWGSOP	Brazil	197
Gastric cancer (25)	Negative								EWGSOP	Mexico	628
Prostate cancer (26)	Negative	4.87°		0.77					AWGS2019	Korea	119
Solid and hematologic cancer (27)	Negative	4°							SARC-F questionnaire	Brazil	124
Non-small cell lung cancer and GI cancer (28)	Negative	4.25°		0.785					AWGS2019	China	445
Non-cancer											
Cardiovascular diseases (35)	Negative	4.55°	4.25°	0.821/0.777	76%	61.4%	74%	86.8%	AWGS	Japan	412
After cardiovascular surgery (37)	Negative								AWGS	Japan	144
Acute stroke (38)	Negative	5.28°	4.62°	0.829					AWGS	Japan	140
Recover from stroke (39)	Negative	4.76°	4.11°	0.849/0.832	80%	73.5%	79%	82.9%	AWGS	Japan	577
Parkinson's (40)	None								EWGSOP 2019	Northeastern Brazil	77
CKD (41)	Negative								AWGS	Korea	149
ND-CKD (42)	Negative								EWGSOP 2019	Brazil	139
Kidney transplant (43)	Negative	4.46°		0.96	74%		70%		AWGS	Japan	210
Kidney transplant (44)	None								EWGSOP	Brazil	129
Maintenance hemo-dialysis (45)	Negative	4.67°	4.60°	0.82/0.83	87.93%	85.45%	69.03%	66.67%	AWGS	China	346
Cirrhosis (46)	Negative	5.6°	5.4°	0.748/0.677	94%	39%	94%	74%	SMI $\leq$ 50 cm^2/m^2 for men SMI $\leq$ 39cm^2/m^2 for women	American	463
COPD (47)	Negative								EWGSOP	Italy	263
PD (48)	Negative	4.4°		0.73	81.3%		59.6%		AWGS	Korea	200
Community-dwelling people											
Adults of ≥50 years old (50)	Negative with pre-sarcopenia	5.42°	4.67°	0.821/0.836					EWGSOP 2019	Poland	1567
Adults of 50–64 years old (53)	Negative	4.3°		0.9306	91.95%		66.77%		EWGSOP 2019	Mexico	498
Adults of ≥65 years old (53)		4.1°		0.7930	72.76%		73.81%			Mexico	
Adults of ≥65 years old (51)	Negative								The loss of muscle mass at a rate of 1–2% per year	Italy	207
Physically active older women (54)	None								EWGSOP	Brazil	94
Women of ≥60 years old (52)	Negative								EWGSOP 2019	Mexico	250
Older adults (49)	Negative	4.05°	3.55°	0.825/0.796					AWGS	Japan	285

AUROC, area under the receiver operating characteristic; SMI, skeletal muscle index; PD, Peritoneal dialysis; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ND-CKD, Non-dialysis Chronic Kidney Disease; AWGS, Asian Working Group for Sarcopenia 2019; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP 2019, European Working Group on Sarcopenia in Older People 2019.

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observing a weak correlation between low PhA and sarcopenia (OR = 1.50 (CI: 0.520–4.319; $P < 0.01$), as well as muscle mass, grip strength, and walking speed (54).

Discussion

Based on the results above (Table 1), we find that, in terms of cancer, low PhA is associated with sarcopenia risk in patients, particularly in gastric cancer (25), colorectal cancer (24), and prostate cancer (26). However, PhA has only been proven to be associated with malnutrition rather than sarcopenia in some types of cancers (29–34). As patients with breast cancer are at lower risk of malnutrition and sarcopenia, no conclusions can be drawn on the associations between PhA and sarcopenia (29).

Moreover, we can ascertain that PhA has a strong negative relationship with sarcopenia in some non-cancer diseases (35, 37–39, 41–43, 45–48), whereas irrelevant results were found for Parkinson's (40) and kidney transplant (44) patients. Although muscle mass is reduced by prolonged paralysis in patients suffering from Parkinson's, the distribution of intracellular and extracellular water remains unchanged. Therefore, no relationship has been found between sarcopenia and PhA. As for patients who have received kidney transplants, the long-term use of immunosuppressants and hormone drugs may destroy the integrity of the cell membrane, making reactance measurement impossible, as well as sarcopenia prediction.

After comparing studies in community-dwelling people that can illustrate the negative relationship between PhA and sarcopenia with those that cannot, we speculate that the differences may be due to the sample sizes of the models (1567 vs. 94) and the different populations. Other reasons may include differences in age, sex ratios, adiposity, diagnostic methods for sarcopenia (EWGSOP vs. AWGS), measurement conditions, and equipment.

Therefore, the current research examining the utility of PhA as a marker for predicting sarcopenia has a few limitations. (1) We found that owing to the characteristics of the specific device used for measuring PhA, there may be deviations when it is measured by different devices. Additionally, there is no universal standard for the condition of the individual when measuring PhA, such as whether they are measured in the morning, whether they are measured in a fasting state, and whether they are measured while urinating, and these differences may reduce the predictive value of PhA. There are also population-specific factors that can affect PhA measurement. Therefore, when cutoff values are used to diagnose sarcopenia, researchers need to consider these factors. With this in mind, sample sizes really need to be expanded in future studies so that more accurate and reliable cutoff values can be obtained; this will allow investigation of whether sample size can change the predictive value of PhA for sarcopenia in different populations and different conditions. (2) Associations between PhA and sarcopenia were found after adjustment for hydration status in cancer patients. On this basis, as PhA can be determined by sex, age, BMI, inflammation, lifestyle factors, and the ECW/ICW ratio, we speculate that adjusting for these parameters in non-cancer situations can change the relationship between PhA and sarcopenia. (3) Both pre-disease and post-disease studies can be conducted on the same subjects to verify whether PhA can predict the occurrence of sarcopenia, and determine whether the cutoff point is the same. (4) Additionally, studies investigating whether PhA can predict pre-sarcopenia and sarcopenia are needed in the future. (5) For people with or without the disease, most of the current research still focuses on older adults over the age of 60; however, most people start to lose muscle mass and function around the age of 40 (1). Therefore, further studies are needed to determine whether sarcopenia can be predicted by PhA in middle age.

Conclusion

In conclusion, an increasing number of studies suggest that BIA-derived PhA is an emerging and reliable predictor of sarcopenia in people with many different types of cancer; however, its association with non-cancerous conditions is still unclear. Therefore, further studies with larger sample sizes and different patient groups are required to determine the cutoff value for PhA screening for pre-sarcopenia and sarcopenia and evaluate its association with disease outcomes and prognosis.

Author contributions

Conception and design and administrative support: QZ. Provision of study materials or patients and collection and assembly of data: PD, PY, YT, and HW. Data analysis and interpretation: PD and HW. Revise the manuscript: JW. Manuscript writing and final approval of manuscript: All authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of malnutrition evaluated by the mini nutritional assessment on the prognosis of acute hospitalized older adults

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Background: Malnutrition is prevalent among hospitalized older patients. Therefore, this study aimed to investigate the association between nutritional status [assessed using the Mini Nutritional Assessment (MNA) and serum albumin levels] and adverse outcomes in hospitalized older patients. We also aimed to compare the predictive utility of our findings.

Methods: This retrospective cohort study was conducted between January 2016 and June 2020. In total, 808 older patients (aged $\geq$ 65 years, mean age 82.8 $\pm$ 6.70 years, 45.9% male) admitted to the acute geriatric unit were included in our sample. Comprehensive geriatric assessments, including the MNA, were performed. Malnutrition and risk of malnutrition were defined as MNA $<$ 17, albumin $<$ 3.5 g/dL and 17 $\leq$ MNA $\leq$ 24, 3.5 g/dL $\leq$ albumin $<$ 3.9 g/dL, respectively. The primary outcome was that patients could not be discharged to their own homes. The secondary outcomes were overall all-cause mortality, 3-month all-cause mortality, and incidence of geriatric syndrome, including delirium, falls, and newly developed or worsening pressure sores during hospitalization.

Results: Poor nutritional status was associated with older age; female sex; admission from the emergency room; high risk of pressure sores and falls; lower physical and cognitive function; higher depressive score; and lower serum albumin, protein, cholesterol, and hemoglobin levels. In the fully adjusted model, malnutrition assessed using the MNA predicted discharge to nursing homes or long-term care hospitals [odds ratio (OR) 5.822, 95% confidence interval (CI): 2.092–16.199, P = 0.001], geriatric syndrome (OR 2.069, 95% CI: 1.007–4.249, P = 0.048), and 3-month mortality (OR 3.519, 95% CI: 1.254–9.872, P = 0.017). However, malnutrition assessed using albumin

levels could only predict 3-month mortality (OR 3.848, 95% CI: 1.465–10.105, $P = 0.006$). The MNA predicted 3-month mortality with higher precision than serum albumin levels ($P = 0.034$) when comparing the areas under the receiver operating characteristic curve.

Conclusion: Nutritional risk measured by the MNA was an independent predictor of various negative outcomes in hospitalized older patients. Poor nutritional status assessed by serum albumin levels, the most widely used biochemical marker, could predict mortality, but not the development of geriatric syndrome or discharge location reflecting functional status.

KEYWORDS

nutrition, discharge location, geriatric syndrome, mini nutritional assessment, serum albumin

1. Introduction

Malnutrition is an imbalance between food intake and body requirements, which results in altered metabolism, impaired function, and loss of body mass (1, 2). Malnutrition is common in older adults (3). People eat less and make different food choices as they age (4). Age-related physiological changes, including slower gastric emptying, changes in hormonal responses, and altered taste and smell, can contribute to decreased food intake (5). Other factors such as marital status, income, education, and socioeconomic status may also influence eating habits among older adults (6).

Studies have shown that malnutrition has serious implications for recovery from disease and is associated with increased morbidity and mortality (2, 7). Malnourished older adults tend to have higher rates of complications and infections, as well as longer hospital stays (8, 9).

Poor nutritional status is also associated with geriatric syndrome (10). Undernutrition is a cornerstone in the concept of the cycle of frailty, a self-aggravating cycle of negative energy balance, and the cause of decreased physical activity and a further decline in physical performance (11, 12). Previous studies have confirmed that malnutrition contributes to the development of delirium and pressure sores in hospitalized older patients (13, 14). Additionally, malnutrition at the time of hospital admission is a major risk factor for in-hospital falls (15).

The likelihood of patients being alive and in their own homes after hospital discharge is an important goal in the care of hospitalized older patients (16). After acute hospitalization, frail older adults are more likely to be admitted to nursing facilities due to their dependency on assistance with activities of daily living (ADL) (17, 18). However, institutionalization often leads to a more rapid deterioration of function due to the perpetual bedridden state (19, 20). While the location of discharge after acute geriatric hospitalization is an important issue in older patients, studies on the association between nutritional status and discharge location are limited.

As comprehensive nutritional assessment is complex and time consuming, several screening tools are used to assess nutritional status. For instance, the Mini Nutritional Assessment (MNA) is a validated test recommended for nutritional screening in older populations and has been widely used in different clinical settings (21, 22). The MNA is a practical, non-invasive tool that allows rapid evaluation of the nutritional status of older adults (23, 24). Various studies on the association between malnutrition and clinical outcomes in hospitalized older adults using the MNA have been conducted (25, 26). The MNA was useful for predicting frailty in hospitalized older patients (27), and lower MNA scores were significant predictors of post-discharge emergency department visits (28) and mortality outcomes (29–31). However, in another study, malnutrition as diagnosed with the MNA at admission failed to predict long-term mortality in older inpatients (26).

Despite its clinical significance, studies on the predictive role of the MNA in the hospital course and outcomes of acutely hospitalized older patients are scarce. In particular, there is a paucity of studies evaluating the prognostic prediction of the MNA by comparison with widely used biochemical markers. Therefore, we aimed to analyze the efficacy of the MNA in predicting geriatric syndrome, discharge location, and mortality in patients admitted to the Geriatric Center of a university hospital and compared the prognostic utility of the MNA and serum albumin levels.

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study was conducted in Seoul National University Bundang Hospital between January 1, 2016 and June 30, 2020. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital. The requirement for informed

consent was waived because of the retrospective nature of the study, and it was impossible to obtain consent from each participant who had already been discharged (B-2206-760-106).

Older patients (aged ≥ 65 years) who were admitted to the Geriatric Center from their own home and underwent comprehensive geriatric assessment (CGA) were included. If patients were admitted more than once, only the data corresponding to the last admission were analyzed. Patients with incomplete nutritional assessments were excluded.

2.2. Patient assessment

Baseline patient characteristics, including demographic, anthropometric, laboratory data, and admission site (emergency room or outpatient clinic) were retrieved from the electronic medical record systems. The risk of fall and pressure score were evaluated using the Hendrich II Fall Risk Model and Braden Scale (for predicting pressure ulcer risk in routine nursing practice) (32, 33). The CGA, a multidisciplinary and interdisciplinary process, is the accepted gold standard for the care of older, frail, hospitalized patients. The CGA consists of medication assessment, comorbidity, muscle strength, cognitive function, depression, and nutrition. Medication lists were reviewed by a pharmacist, and a potentially inappropriate medication (PIM) list was assessed using the PIM list defined in the COMPASS (COMPrehensive geriatric AsseSSment and multidisciplinary team intervention for hospitalized older adults) study (34). The burden of comorbidity was quantified using the Charlson comorbidity index (CCI), which contains 19 categories of chronic diseases (35). Muscle strength was assessed by the handgrip strength in the dominant hand with the patient in the sitting position with elbows flexed at 90° or in the supine position if patients were unable to maintain a sitting position. Handgrip strength was measured using a Jamar Plus + Digital Hand Dynamometer (Patterson Medical). Handgrip strength was measured twice and the maximum value was used for analysis (36, 37). Cognitive function was measured using the Korean version of the Mini-Mental State Examination-2 (38). Depression was assessed using the short form of the Korean Geriatric Depression Scale (39). Nutritional status was defined according to the MNA scores as normal (> 24), risk of malnutrition (17–24), and malnutrition (< 17) (40). Nutritional status was also categorized using the biochemical marker, albumin, according to the serum albumin level: normal (> 3.9 g/dL), risk of malnutrition (3.5–3.9 g/dL), and malnutrition (< 3.5 g/dL) (41).

2.3. Outcome

The primary outcome was that patients could not be discharged to their own homes. The secondary outcomes were overall all-cause mortality, 3-month all-cause mortality after discharge, and incidence of geriatric syndrome during hospitalization. Incidence of geriatric syndrome was defined as a composite outcome of delirium, falls, and newly developed or worsening pressure sores during hospitalization. Delirium was defined as newly administered medications for delirium symptom control (e.g., haloperidol, quetiapine, or olanzapine) or consultation with the neuropsychiatric department for delirium. Falls were detected using a formal mandatory report for falls in the nursing department. Pressure sores were evaluated using a weekly report for pressure sores, which contained information on the site and grade of the pressure sores documented by the nursing department. Mortality data up to December 12, 2020 were obtained from the Ministry of Security and Public Administration.

2.4. Statistical analysis

Statistical analyses were performed using PASW Statistics software (version 25.0; SPSS Inc.) and MedCalc (MedCalc Software Ltd.). Continuous variables are expressed as means (standard deviations, SDs), and qualitative variables are presented as counts and percentages. Statistical differences were assessed using the one-way analysis of variance or Pearson's chi-square test. The relationship between malnutrition assessed using the MNA or albumin levels and adverse outcomes was determined using (a) age, sex, and body mass index (BMI); (b) age, sex, BMI, and admission site; and (c) a fully adjusted logistic regression model for the relevant prognostic variables. Full adjustment was conducted for age, sex, BMI, admission site, CCI, hemoglobin levels, and creatinine levels. Hazard ratios for all-cause mortality according to nutritional status assessed by the MNA and serum albumin level were analyzed using Cox proportional hazards models. Kaplan–Meier analysis was used for survival curves, and log-rank tests were used to assess significance. We determined the model's predictive value for 3-month mortality after discharge with two malnutrition assessment methods (albumin levels and the MNA) by comparing the areas under the receiver operating characteristic (ROC) curve.

3. Results

During the study period, 1,632 patients (aged ≥ 65 years) were admitted to the Geriatric Center and underwent CGA. Among them, 740 patients were admitted from centers other than their homes (47 from group homes, 274 from nursing homes, 333 from long-term care hospitals, and 86 from hospitals). After excluding 77 rehospitalizations and 7 patients for whom nutritional assessments were not performed, 808 patients were included in the analysis (**Figure 1**).

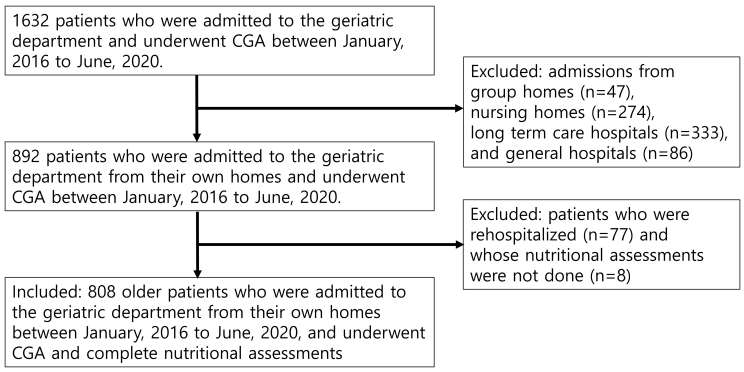

FIGURE 1
Flow of patients through the study. The study participants consisted of 808 older hospitalized patients admitted from their own homes to the geriatric department ward and underwent comprehensive geriatric (CGA) and complete nutritional assessments.

The mean age of the patients was 82.8 years (SD, 6.70) and 45.9% were male. The mean length of hospital stay was 11.3 days (SD, 21.9). Among the patients, 77.8% were admitted through emergency room, and they were followed for an average of 452.5 days (interquartile range, IQR, 148.25–919.75). Among them, 43 patients (5.3%) had in-hospital mortality, 160 (19.8%) had 3-month mortality, and 417 patients (51.6%) had all-cause mortality. One hundred and ninety-eight (24.5%) patients experienced geriatric syndromes of delirium (n = 66, 8.2%), falls (n = 17, 2.1%), and newly developed or worsening pressure sores (n = 134, n = 16.6%). Nineteen patients experienced two types of geriatric syndrome.

We analyzed the relationship between general patient characteristics, including patients' demographic data, laboratory data, and CGA components, according to the nutritional status assessed by the MNA (Table 1). Patients who were malnourished were predominantly older; female; admitted through the emergency room; and had a higher risk of pressure sores and falls, ADL dependency or instrumental activities of daily living (IADL); lower Mini-Mental State Examination (MMSE) score; higher Korean version of the short form of the Geriatric Depression Scale (SGDS-K) score; lower grip strength; and shorter mid-arm circumference (MAC) and calf circumference (CC). Patients with poor nutrition tended to have lower serum albumin, protein, cholesterol, and hemoglobin levels (Table 1).

The relationship between malnutrition status assessed using the MNA and serum albumin levels and outcomes was analyzed using multilevel multiple logistic regression. The fully adjusted odds ratios (ORs) for discharge to nursing homes or long-term care hospitals were 4.271 (95% CI: 1.499–12.170, P = 0.042) for the risk of malnutrition and 5.822 (95% CI: 2.092–16.199, P = 0.001) for malnutrition compared to normal nutritional status assessed by the MNA (Table 2). However, nutritional status assessed by serum albumin level could not predict discharge to nursing home or long-term care hospitals with ORs of 1.751 (95% CI: 0.771–0.377, P = 0.181) for risk of malnutrition and 2.164 (95% CI: 0.993–4.715, P = 0.052) for malnutrition compared to normal nutritional status (Table 3). In the fully adjusted model, only malnutrition status assessed by the MNA showed statistical significance in predicting geriatric syndrome, with an OR of 2.069 (95% CI: 1.007–4.249, P = 0.0480) (Table 2). Malnutrition status assessed by both the MNA and serum albumin level could predict 3-month all-cause mortality after discharge with ORs of 3.519 (95% CI: 1.254–9.872, P = 0.017) and 3.848 (95% CI: 1.465–10.105, P = 0.006), respectively (Tables 2, 3). Both risk of malnutrition and malnutrition assessed by the MNA and serum albumin level was associated with all-cause mortality (Table 4).

To assess the prognostic utility of malnutrition assessed by the MNA and serum albumin levels, we conducted a Kaplan–Meier analysis (Figure 2). Malnutrition assessment according to the MNA and serum albumin levels successfully predicted all-cause mortality; *post hoc* analysis to compare normal vs. risk of malnutrition, normal vs. malnutrition, and risk of malnutrition vs. malnutrition showed that they were all statistically significant in both assessments.

The MNA predicted 3-month all-cause mortality more accurately than the serum albumin levels according to the comparison of the area under the ROC curve (AUC). The AUCs for the predictive model according to the MNA and albumin levels were 0.739 (95% CI: 0.707–0.769) and 0.686 (95% CI: 0.653–0.718), respectively. The pairwise comparison of the AUC was statistically significantly different between the MNA and serum albumin levels (P = 0.034) (Figure 3).

4. Discussion

Our study shows that malnutrition status defined by the MNA was significantly associated with adverse outcomes in older patients hospitalized in acute geriatric centers. Older

inpatients with malnutrition were five times more likely to be discharged to nursing homes or long-term care hospitals and three times more likely to die within 3 months. Additionally, their chance of developing geriatric syndrome during hospitalization more than doubled.

Frailty, as a reflection of decreased physiological reserve, is closely associated with biological age (42), concurrent medical conditions, morbidity, and decreased survival in older adults (43). In frailty assessments, parameters reflecting nutritional status are commonly included, as malnutrition is considered a key factor in the progression of frailty (11, 12). The addition of a stressor event such as pneumonia or urinary tract infection to a frail older person with impairment of balance or cognition explains the geriatric syndromes of falls and delirium, respectively, as consequences of the loss of homeostatic reserve (44). Unintentional weight loss, a representative criterion for the frailty phenotype model (11), is a major risk factor for pressure sore development (14).

There are various definitions for aging in place, but it generally refers to the phenomenon of older adults that remain living within their communities with some level of independence, rather than in residential care (45). One of the biggest threats to aging in place is that older adults become ADL-dependent due to functional decline after acute disease. In our study, there was a significant difference in the ADL score according to nutritional status. Therefore, it is understandable that nutritional status can influence the discharge location.

In the past, serum albumin was widely used as an indicator of malnutrition in older patients (46, 47). It is well known that serum albumin levels are an independent risk factor for all-cause mortality in older adults (48). Our models also showed that serum albumin levels could predict 3-month all-cause mortality after discharge. However, nutritional status evaluated using the MNA showed a significant association with discharge location and geriatric syndrome, whereas nutritional status evaluated using serum albumin had no significant association. This may be because the MNA has the advantage of predicting functional decline (49, 50). The fact that the MNA is a multidimensional tool that includes general assessment, dietary assessment, and anthropometric assessment can make this prediction possible (23). Representatively, CC included in the MNA is used to screen for sarcopenia (51, 52), a major cause of functional

TABLE 1 General patient characteristics and results of the comparison of patients' nutritional status assessed by MNA.

	Total (n = 808)	Normal (n = 98, 12.1%)	Risk of malnutrition (n = 284, 35.1%)	Malnutrition (n = 426, 52.7%)	p
Age (years)	82.8 (6.7)	81.7 (6.2)	81.6 (6.4)	83.9 (6.8)	<0.001
Sex (male)	371 (45.9%)	59 (60.2%)	120 (42.3%)	192 (45.1%)	0.008
BMI (kg/m^2)	21.6 (4.5)	26.3 (3.9)	23.4 (3.5)	19.4 (3.8)	<0.001
Admission site (emergency room)	629 (77.8%)	71 (72.4%)	204 (71.8%)	354 (83.1%)	0.001
Length of hospital stay	11.6 (21.9)	8.6 (13.9)	10.1 (9.9)	13.4 (28.2)	0.052
Hendrich scale	6.2 (2.8)	4.7 (2.6)	5.7 (2.6)	6.8 (2.8)	<0.001
Braden scale	16.2 (3.9)	19.2 (2.9)	17.7 (3.4)	14.5 (3.5)	<0.001
CCI (score)*	2.4 (1.9)	2.1 (1.8)	2.4 (2.0)	2.4 (1.9)	0.289
ADL (score)†	65.4 (39.8)	97.2 (8.7)	85.5 (26.5)	44.6 (39.8)	<0.001
IADL (score)‡	3.1 (2.6)	5.3 (1.8)	4.5 (2.4)	1.7 (2.1)	<0.001
SGDS-K (score)ǁ	5.5 (3.6)	3.6 (2.7)	5.9 (3.6)	6.8 (3.9)	<0.001
MMSE (score)§	11.3 (10.0)	21.5 (5.5)	16.1 (8.3)	5.7 (8.0)	<0.001
Grip strength (kg)¶	16.7 (8.0)	22.4 (8.7)	17.0 (6.8)	13.0 (6.8)	<0.001
MAC (cm)**	23.1 (3.6)	26.2 (2.9)	24.4 (2.8)	21.6 (3.4)	<0.001
CC (cm)**	28.1 (4.4)	33.2 (3.8)	30.1 (3.1)	25.7 (3.5)	<0.001
Number of medications	10.0 (5.3)	10.5 (6.3)	9.7 (5.2)	10.1 (5.0)	0.449
Number of PIMs	0.27 (0.54)	0.30 (0.56)	0.24 (0.51)	0.28 (0.56)	0.614
Albumin (g/dL)	3.2 (0.6)	3.6 (0.5)	3.4 (0.6)	3.0 (0.6)	<0.001
Protein (g/dL)	6.4 (0.9)	6.6 (0.9)	6.5 (0.9)	6.3 (0.9)	<0.001
Cholesterol (mg/dL)‡	133.7 (43.4)	139.3 (42.7)	137.8 (42.8)	129.7 (43.7)	0.020
Hemoglobin (g/dL)	11.5 (2.2)	12.1 (1.9)	11.5 (2.1)	11.3 (2.3)	0.002
Creatinine (mg/dL)	1.5 (1.4)	1.2 (0.5)	1.5 (1.3)	1.5 (1.6)	0.158

*n = 801, †n = 805, ‡n = 806, §n = 618, ǁn = 251, ¶n = 460, **n = 787.

ADL, activities of daily living; CC, calf circumference; CCI; Charlson's comorbidity index; IADL, instrumental activities of daily living; MAC, mid arm circumference; MMSE, mini-mental status examination; SGDS-K, short form of the Korean Geriatric Depression Scale; PIM, potentially inappropriate medication.

Statistical difference was assessed by one-way analysis of variance or Pearson's chi-squared test.

TABLE 2 Odds ratios for incident geriatric syndrome, discharge location and 3-months mortality according to nutritional status assessed by MNA.

	Model 1*	Model 2†	Model 3‡
Geriatric syndrome			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.210 (0.600–2.442) *P* = 0.595	1.196 (0.594–2.408) *P* = 0.615	1.136 (0.553–2.331) *P* = 0.728
Malnutrition	2.299 (1.140–4.633) ***P = 0.020***	2.268 (1.122–4.585) ***P = 0.023***	2.069 (1.007–4.249) ***P = 0.048***
Discharge to nursing home or long-term care hospital			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	4.277 (1.549–11.805) ***P = 0.005***	4.131 (1.504–11.346) ***P = 0.006***	4.271 (1.499–12.170) ***P = 0.007***
Malnutrition	6.644 (2.432–18.147) ***P < 0.001***	6.587 (2.401–18.073) ***P < 0.001***	5.822 (2.092–16.199) ***P = 0.001***
3-months mortality			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	3.685 (1.260–10.782) ***P = 0.017***	3.573 (1.223–10.438) ***P = 0.020***	2.468 (0.806–7.556) *P* = 0.114
Malnutrition	3.931 (1.421–10.875) ***P = 0.008***	3.842 (1.388–10.635) ***P = 0.010***	3.519 (1.254–9.872) ***P = 0.017***

Data are presented as odds ratio (95% confidence interval).
*Adjusted by age, sex, body mass index.
†Adjusted by age, sex, body mass index and admission site.
‡Adjusted by age, sex, body mass index, admission site, CCI, hemoglobin and creatinine.
Values in bold and italic indicate statistical significance.

TABLE 3 Odds ratios for incident geriatric syndrome, discharge location, and 3-months mortality according to nutritional status assessed by albumin.

	Model 1*	Model 2†	Model 3‡
Geriatric syndrome			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.749 (0.884–3.460) *P* = 0.108	1.014 (0.969–1.061) *P* = 0.553	1.713 (0.853–3.440) *P* = 0.130
Malnutrition	1.964 (1.046–3.689) ***P = 0.036***	1.657 (0.872–3.148) *P* = 0.123	1.753 (0.899–3.419) *P* = 0.099
Discharge to nursing home or long-term care hospital			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.652 (0.743–3.675) *P* = 0.218	1.601 (0.718–3.573) *P* = 0.250	1.751 (0.771–3.77) *P* = 0.181
Malnutrition	2.630 (1.267–5.457) ***P = 0.009***	2.065 (0.978–4.362) *P* = 0.057	2.164 (0.993–4.715) *P* = 0.052
3-months mortality			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.599 (0.552–4.403) *P* = 0.402	1.379 (0.481–3.952) *P* = 0.549	1.443 (0.484–4.306) *P* = 0.511
Malnutrition	4.338 (1.694–11.113) ***P = 0.002***	4.006 (1.556–10.317) ***P = 0.004***	3.848 (1.465–10.105) ***P = 0.006***

Data are presented as odds ratio (95% confidence interval).
*Adjusted by age, sex, body mass index.
†Adjusted by age, sex, body mass index and admission site.
‡Adjusted by age, sex, body mass index, admission site, CCI, hemoglobin and creatinine.
Values in bold and italic indicate statistical significance.

TABLE 4 Hazard ratios for all-cause mortality according to nutritional status assessed by albumin and MNA.

	Model 1*	Model 2†	Model 3‡
Albumin			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.682 (1.062–2.663) ***P = 0.027***	1.605 (1.011–2.547) ***P = 0.045***	1.638 (1.023–2.623) ***P = 0.040***
Malnutrition	2.680 (1.759–4.082) ***P < 0.001***	2.588 (1.694–3.953) ***P < 0.001***	2.632 (1.702–4.071) ***P < 0.001***
MNA			
Normal (reference)	Reference	Reference	Reference
Risk of malnutrition	1.831 (1.172–2.858) ***P = 0.008***	1.832 (1.175–2.858) ***P = 0.008***	1.599 (1.019–2.509) ***P = 0.041***
Malnutrition	2.693 (1.729–4.193) ***P < 0.001***	2.669 (1.714–4.157) ***P < 0.001***	2.341 (1.489–3.381) ***P < 0.001***

Data are presented as hazard ratio (95% confidence interval).
*Adjusted by age, sex, body mass index.
†Adjusted by age, sex, body mass index and admission site.
‡Adjusted by age, sex, body mass index, admission site, CCI, hemoglobin and creatinine.
Values in bold and italic indicate statistical significance.

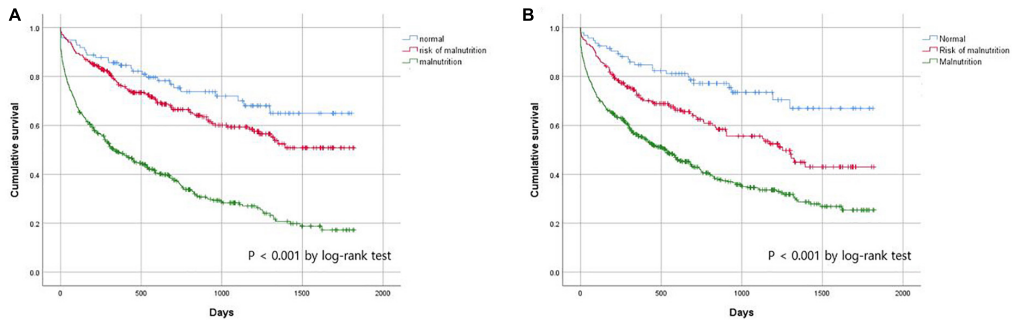

FIGURE 2
Cumulate survival rate according to nutritional status assessed by **(A)** MNA and **(B)** albumin.

decline in older adults (53, 54). Because functional decline is closely associated with mortality (55, 56), it is reasonable that the MNA is a better predictor of post-discharge mortality than serum albumin levels. Recent studies showed that MNA is also useful to detect frailty status in older adults (26, 57).

From our observations, we posit that nutritional status should be considered when establishing a protocol for treating acute hospitalized older patients to prevent adverse outcomes, such as death and nursing facility admission. With nutrition comprising the core element of multidimensional frailty preventative measures, it is necessary to maximize the potential benefits of nutritional support programs; further nutritional intervention studies on acute-hospitalized older patients are warranted. In our study group, cut-off points to predict 3 months mortality was MNA score $\leq$ 14 according to highest Youden index, with a sensitivity of 71.5% and specificity of 67.5%, while positive predictive value and negative predictive value were 34.14 and 90.97%, respectively. The cut-off point would be useful to identify the high-risk patients who can benefit from nutritional support program.

This study has several strengths. First, the analysis of the impact of malnutrition on clinical outcomes included the discharge location, and statistically significant results

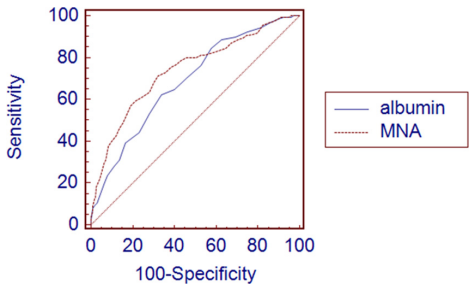

FIGURE 3
Comparison of area under receiver operating characteristic curve between albumin and MNA for 3-month all-cause mortality after discharge. Graph shows higher AUC in MNA 0.739 (0.707–0.769) than albumin 0.686 (0.653–0.718) with significant *P*-value of 0.034.

were obtained even after adjusting for multiple covariates. Second, by analyzing the impact of nutritional status in acute geriatric patients, malnutrition was identified as a target for interventional studies to improve the clinical outcomes of hospitalized older adults. This study also has some limitations. First, because this study was conducted in inpatients at a university hospital, it is difficult to support the generalization of the study. Second, in some cases, the various circumstances of caregivers may influence the decision of discharge location for older patients. However, factors related to caregivers were not included in this analysis. Third, serum albumin has a limitation in that it is difficult to accurately evaluate the nutritional status of patients in the acute phase. Current paper recommends that serum albumin must be correctly recognized as an inflammatory marker associated with "nutritional risk" in nutrition assessment and should not be inappropriately interchanged with concept of malnutrition (58). However, serum albumin was traditionally considered a useful biochemical laboratory value in nutritional assessment and currently there is a lack of biomarkers widely used to replace it. Therefore, in our retrospective design study, serum albumin was used as a clinically widely used biomarker measured in all study participants.

In conclusion, nutritional status evaluated using the MNA was an independent predictor of various negative outcomes among older hospitalized patients. Poor nutritional status assessed by serum albumin levels, the most widely used biochemical marker, could predict mortality, but not geriatric syndrome or discharge location, which might reflect the patients' functional decline. As a multidimensional tool, the MNA needs to be used more actively for the nutritional assessment of geriatric patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

K-IK: conceptualization and funding acquisition. J-YC: data curation and formal analysis. M-GK, J-YC, H-JY, S-YP, YK, JK, S-WK, and C-HK: investigation and project administration. K-IK and J-YC: methodology and validation. K-IK and C-HK: supervision. M-GK and J-YC: visualization, roles, and writing—original draft. M-GK, J-YC, and K-IK: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic nutritional index: A potential biomarker for predicting the prognosis of decompensated liver cirrhosis

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Background: Prognostic nutritional index (PNI) is an independent predictor of the prognosis of various diseases. However, the prognosis value of PNI in patients with decompensated liver cirrhosis (DLC) remains unknown. The study aimed to investigate the prognostic significance of PNI in patients with DLC.

Methods: A total of 214 eligible patients were enrolled in the study's development cohort between January 2018 and March 2021. The clinical primary study endpoints were mortality at 3 and 6 months. Receiver operating characteristic (ROC) curve analysis was used to assess the PNI's prediction accuracy, and Youden's index was utilized to determine the PNI's optimal cut-off value. Moreover, based on the optimal cut-off value, patients were categorized into high and low PNI groups. Multivariate logistic regression analysis was used to determine independent risk factors for mortality, while the relationship between PNI and the risk of death was identified and demonstrated using restricted cubic splines (RCS). A validation cohort of 139 patients was to verify the predictive power of the PNI.

Results: In the development cohort, the mortality rate at 3 and 6 months were 10.3% (22) and 14.0% (30), respectively. The PNI had comparable predictive power with the MELD score at all follow-up endpoints. Decreased PNI was an independent predictor of adverse prognosis at all follow-up endpoints. The RCS revealed a linear correlation between PNI and the risk of death. We confirmed that lower PNI was an independent predictor of poor prognosis in the validation cohort.

Conclusion: The findings showed that lower PNI is an independent factor of poor outcomes and might be utilized as a potentially promising prognostic predictor in patients with DLC.

KEYWORDS

decompensated liver cirrhosis, prognostic nutritional index, prognostic factor, mortality, independent predictor, validation

Introduction

Liver cirrhosis possesses a significant global morbidity and mortality rate, resulting in a million deaths annually, and is the 11th leading cause of death globally (1, 2). As compensated liver cirrhosis is difficult to identify, most patients are diagnosed with decompensated liver cirrhosis (DLC) in the hospital due to numerous complications (3). DLC has an unfavorable prognosis, with a median survival time of approximately 2 years, placing a heavy financial burden on healthcare (4). Despite the availability of several therapies, the mortality rate remains high for patients with DLC (5, 6). As a result, there is a need for a practical and simple predictor to evaluate the risk of death in patients with DLC in order to improve clinical management and subsequently reduce mortality.

Prognostic Nutritional Index (PNI) is a simple and objective index of inflammatory and nutrition status derived from serum albumin (ALB) and lymphocyte counts. Recently, PNI has been reported to be an independent prognostic predictor for patients with cancer, stroke, heart disease, chronic kidney disease, acute exacerbation of the chronic obstructive pulmonary disease, sepsis, COVID-19, and autoimmune disease (7–17). However, no research has been conducted to examine the relationship between PNI and the prognosis of patients with DLC. Several studies have shown that systemic inflammatory response and malnutrition are associated with poor prognosis in patients with liver cirrhosis (18–24). Hence, it seems reasonable to hypothesize that there may be a significant correlation between PNI and the risk of death in patients with DLC when PNI is used as an indicator of inflammatory and nutrition status. The current study aimed to evaluate the prognostic role of PNI in patients with DLC.

Materials and methods

Patient population

Between January 2018 and March 2021, we recruited patients with DLC who were admitted to the Department of Gastroenterology, Yijishan Hospital of Wannan Medical College as the development cohort of the study. We enrolled patients with DLC attending the Yijishan Hospital of Wannan Medical College between April 2021 and February 2022 as the validation cohort. DLC was defined as biochemical, clinical, endoscopic manifestations, imaging signs, and complications of ascites, gastrointestinal bleeding, hepatorenal syndrome, or hepatic encephalopathy (25). Reasons for exclusion were: (1) non-first admission, (2) malignant diseases, (3) cardio-cerebrovascular disease, (4) autoimmune diseases, (5) hyperpyrexia, (6) primary kidney disease, (7) incomplete data, and (8) loss to follow-up. The flow chart of the patient selection process is provided in **Supplementary Figure 1**.

Study variables and outcomes

On admission, variables including sex, age, cause of liver cirrhosis, modes of decompensation, and laboratory variables were collected (**Table 1**). PNI was calculated as serum albumin (ALB) concentration (g/L) + 5 × total lymphocyte count (10^9/L) (16). The Model for End-Stage Liver Disease (MELD) score was utilized to evaluate the severity and prognosis of liver disease (26). The mortality rate at 3 and 6 months was assessed using medical records or direct telephone conversations with patients or their relatives.

Statistical analysis

Categorical data were reported as frequency and percentage, while continuous variables were expressed as means ± standard deviation or medians (25th–75th percentiles). The independent sample *t*-test (normally distributed data) or the Mann-Whitney *U*-test (non-normally distributed data) were used to examine the differences in continuous variables. Categorical data were assessed by the chi-square test (27). Associations between MELD score and PNI were analyzed using Spearman's analysis (28). Multivariate logistic regression analysis was used to determine independent predictors of mortality in patients with DLC. The degree of multicollinearity among the variables was measured by calculating the variance inflation factor (VIF) values, and VIF > 10 was considered to have multicollinearity (29). The diagnostic accuracy of PNI was assessed by analyzing the area under the receiver operating characteristic (ROC) curve (30), and the PNI's optimal cutoff value was determined using Youden's index (31). The values of the area under the ROC curve (AUC) were compared using the DeLong test (32). The patients were then categorized into high and low groups based on the optimal cut-off value. The Kaplan-Meier analysis with log-rank test was used to estimate survival between high and low groups. Furthermore, based on multivariate analysis, restricted cubic spline (RCS) was applied to assess the non-linear association between the PNI and the risk of death (33). The number of knots between three and five was chosen based on the minimum value for the Akaike information criterion to obtain the best fit and avoid overfitting in the main splines (34). Two-side P-value < 0.05 was considered statistically significant. The SPSS (version 25.0), R (version 4.0.2), and MedCalc (Version 15.2) were used to perform the statistical analyses in the study.

Results

Study population

A total of 353 patients with DLC who met the inclusion criteria were recruited for the study. In the development cohort,

ascites (84.6%) were found to be the most common type of decompensation, followed by variceal bleeding (32.2%), hepatic encephalopathy (4.2%), and hepatorenal syndrome (2.3%). Cirrhosis was caused by chronic hepatitis B virus in most cases, and the patients' average age was 61.4 ± 12.9 years. The mortality rate at 3 and 6 months were 10.3 and 14.0%, respectively. The baseline characteristics of patients in the development and validation cohort are shown in **Table 1** and **Supplementary Figure 2**.

Clinical and laboratory characteristics between non-survivors and survivors

In the development cohort, the PNI and ALB of the survivor were significantly higher than the non-survivor, while the white blood cell (WBC), platelet (PLT), and MELD scores of the survivor were considerably lower than the non-survivor at any phase of the follow-up ($P < 0.05$). At all follow-up endpoints, no significant differences were found between the two groups in lymphocyte (LYM), hemoglobin (HGB), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ–glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine (Cr), and gender. The clinical and laboratory characteristics between non-survivors and survivors in the development and validation cohort are shown in **Table 1**.

Clinical and laboratory characteristics in high and low PNI groups

In the development cohort, patients were categorized into two groups based on Youden's index, with cut-off values of 35.47 at 3, and 6 months. Patients in the low PNI group were significantly associated with increased mortality, TBIL, PT, and MELD score, and decreased LYM, ALB, and HGB compared to those of the high PNI group at all follow-up endpoints (**Table 2**). Furthermore, a negative correlation was found between PNI and MELD score ($r = -0.41$, $P < 0.001$) (**Figure 1**). In addition, the clinical and laboratory characteristics of patients in the high and low PNI groups in the validation cohort are shown in **Table 2**.

Low PNI as an independent factor of poor prognosis in patients with DLC

Kaplan-Meier analyses showed that mortality was significantly higher in patients with low PNI group than that of in patients with high PNI group (**Supplementary Figure 3**). In multivariate logistic regression analysis, lower PNI was identified as an independent predictor of adverse outcomes in patients with DLC in the development cohort after adjusting for the effect of confounders on mortality at 3, and 6 months, respectively (**Table 3**). The ROC analysis demonstrated that the AUC values of PNI and MELD scores were comparable at 3 months (0.684 vs. 0.683). The AUC values of PNI were higher than the MELD score (0.698 vs. 0.636) at 6 months, but the difference was not statistically significant (Delong test P-value > 0.05) (**Figure 2**).

Linear relationship between the PNI and risk of death

A linear association was observed between the PNI and the risk of death at all follow-up time points (all P for non-linearity > 0.05) (**Figure 3**). PNI was found to be negatively associated with the risk of death, indicating that the risk of death increased with the decrease in PNI.

Verification of the predictive power of the PNI

In the validation cohort, we confirmed that the PNI was an independent predictor of 3- and 6-month mortality in patients with DLC (**Table 3**). In addition, the ROC analysis demonstrated that the PNI had a comparable predictive ability with the MELD score (All Delong test P-value > 0.05) (**Supplementary Figure 4**).

Discussion

The findings demonstrated that lower PNI was an independent predictor for adverse outcomes at all follow-up endpoints and PNI had a potential predictive value for mortality in patients with DLC. Furthermore, a linear correlation between PNI and the risk of death was observed, indicating that mortality increased with the decrease in PNI. Currently, the MELD score is the most extensively used scoring system for stratifying disease severity and predicting mortality in advanced liver disease but requires complicated calculations that are inconvenient for clinical practice (26). In contrast, PNI is a straightforward, effective, and simple index that uses serum albumin level and total lymphocyte count (8). Our findings revealed a significant negative correlation between PNI and MELD scores, and indicated that PNI had comparable predictive power to MELD score at all follow-up endpoints. Previous research found some inflammatory and nutrition indicators, such as the albumin-bilirubin scores, the international normalized ratio-to-albumin ratio, the neutrophil-to-albumin ratio, and the neutrophil-to-lymphocyte ratio, were independent predictors of mortality in patients with liver cirrhosis (35–38). To our knowledge, this is the first study which identified that PNI could be used as an independent predictor for mortality in patients with DLC.

TABLE 1 Clinical and laboratory characteristics of the decompensated liver cirrhosis patients in the development and validation cohort at the 3-month, and 6-month follow-ups.

Variables	Development cohort							Validation cohort						
	All patients (*n* = 214)	3 months			6 months			All patients (*n* = 139)	3 months			6 months		
		Survivors (*n* = 192)	Non-survivors (*n* = 22)	*P*	Survivors (*n* = 184)	Non-survivors (*n* = 30)	*P*		Survivors (*n* = 123)	Non-survivors (*n* = 16)	*P*	Survivors (*n* = 115)	Non-survivors (*n* = 24)	*P*
Gender (*n*, %)				0.161			0.054				0.830			0.859
Male	127 (59.3%)	117 (60.9%)	10 (45.5%)		114 (62.0%)	13 (43.3%)		73 (52.5%)	65 (52.8%)	8 (50.0%)		60 (52.2%)	13 (54.2%)	
Female	87 (40.7%)	75 (39.1%)	12 (54.5%)		70 (38.0%)	17 (56.7%)		66 (47.5%)	58 (47.2%)	8 (50.0%)		55 (47.8%)	11 (45.8%)	
Age (years)	61.4 ± 12.9	61.1 ± 13.0	64.6 ± 11.7	0.228	60.8 ± 12.7	65.1 ± 13.7	0.094	61.3 ± 12.5	60.3 ± 12.5	68.9 ± 10.1	0.009	60.3 ± 12.8	66.3 ± 10.1	0.016
WBC (10^9/L)	3.8 (2.6–5.4)	3.6 (2.5–5.1)	5.1 (3.9–6.4)	0.004	3.6 (2.5–5.1)	4.5 (3.6–6.6)	0.005	3.8 (2.8–5.9)	3.8 (2.8–5.8)	5.1 (2.7–10.0)	0.138	3.8 (2.8–5.8)	4.6 (2.8–7.5)	0.182
LYM (10^9/L)	0.8 (0.6–1.2)	0.8 (0.6–1.2)	0.9 (0.5–1.2)	0.893	0.8 (0.6–1.2)	0.8 (0.5–1.2)	0.940	1.0 (0.6–1.4)	1.0 (0.6–1.4)	0.8 (0.5–1.2)	0.128	1.0 (0.6–1.5)	0.8 (0.5–1.2)	0.066
HGB (g/L)	96.3 ± 25.4	96.4 ± 24.7	95.9 ± 31.1	0.932	96.3 ± 25.1	96.6 ± 27.3	0.944	93.7 ± 27.7	95.8 ± 27.3	77.5 ± 25.8	0.012	96.7 ± 27.6	79.5 ± 23.6	0.005
PLT (10^9/L)	61.5 (44.0–98.5)	58.0 (43.3–94.0)	92.5 (62.8–152.3)	0.007	57.5 (43.3–90.8)	98.5 (62.8–130.8)	0.004	73.0 (49.0–101.0)	71.0 (48.0–101.0)	88.0 (63.0–115.3)	0.151	73.0 (48.0–102.0)	69.0 (49.5–96.8)	0.789
ALB (g/L)	29.6 ± 6.2	30.0 ± 6.2	26.0 ± 4.9	0.004	30.2 ± 6.1	25.8 ± 5.0	<0.001	29.7 ± 5.6	30.2 ± 5.5	25.6 ± 4.7	0.002	30.5 ± 5.6	25.8 ± 4.1	<0.001
TBIL (μmol/L)	24.8 (16.6–37.5)	24.4 (16.8–36.6)	34.1 (16.5–56.2)	0.170	24.5 (17.4–36.8)	27.1 (15.3–51.5)	0.669	27.8 (17.7–45.6)	27.2 (16.9–45.4)	36.8 (22.0–75.9)	0.160	26.9 (16.9–44.4)	36.1 (22.0–61.9)	0.087
ALT (U/L)	25.0 (16.0–41.0)	25.0 (17.0–41.0)	23.5 (13.3–41.5)	0.465	25.0 (17.0–41.8)	23.0 (14.8–34.3)	0.241	24.0 (16.0–41.0)	25.0 (19.0–45.0)	16.0 (9.3–25.3)	0.002	25.0 (19.0–45.0)	18.0 (10.5–28.3)	0.008
AST (U/L)	34.0 (23.0–58.0)	33.0 (22.3–58.0)	43.0 (26.8–59.8)	0.422	34.0 (22.3–58.0)	32.5 (26.0–55.0)	0.994	35.0 (23.0–60.0)	37.0 (24.0–61.0)	26.5 (18.3–37.8)	0.065	37.0 (24.0–61.0)	28.5 (18.3–44.0)	0.139
GGT (U/L)	54.5 (23.0–145.3)	55.5 (23.5–136.3)	46.5 (18.8–200.3)	0.815	55.5 (25.0–132.5)	47.0 (18.8–214.8)	0.757	44.0 (21.0–98.0)	48.0 (24.0–110.0)	21.0 (12.3–59.3)	0.017	49.0 (24.0–110.0)	21.0 (14.0–59.3)	0.015
BUN (mmol/L)	5.4 (4.2–8.0)	5.4 (4.2–7.7)	8.1 (4.3–11.9)	0.084	5.4 (4.2–7.7)	6.5 (4.6–11.9)	0.131	6.3 (4.7–9.6)	6.0 (4.5–8.9)	10.1 (7.0–13.4)	0.001	5.9 (4.3–8.9)	9.5 (6.1–11.7)	0.001
Cr (μmol/L)	67.3 (56.0–85.3)	67.3 (55.9–84.4)	69.7 (54.2–120.4)	0.383	67.3 (56.1–84.3)	68.1 (54.4–104.7)	0.532	59.2 (47.4–81.0)	58.7 (47.0–76.5)	75.6 (55.1–133.8)	0.021	58.7 (46.7–76.4)	69.9 (54.2–117.4)	0.032
PT (S)	14.6 (13.3–16.2)	14.4 (13.2–16.2)	15.7 (14.4–17.2)	0.050	14.4 (13.3–16.1)	15.7 (13.1–19.2)	0.080	15.1 (13.8–16.6)	14.9 (13.7–16.5)	15.9 (14.7–17.9)	0.016	14.8 (13.4–16.2)	15.9 (15.1–18.9)	0.002
PNI	34.6 ± 6.7	35.0 ± 6.6	31.1 ± 7.0	0.01	35.1 ± 6.6	31.0 ± 6.7	0.002	34.2 (30.6–39.8)	35.2 (31.3–40.2)	30.2 (26.6–33.6)	<0.001	35.8 (31.6–40.5)	30.4 (27.8–32.9)	<0.001
MELD score	11.2 (9.1–13.6)	11.2 (9.0–13.2)	14.1 (10.6–17.9)	0.005	11.2 (9.0–13.0)	13.6 (10.0–17.3)	0.017	11.5 (9.0–14.9)	10.9 (9.0–14.3)	15.4 (12.1–21.1)	0.002	10.7 (9.0–14.3)	14.2 (11.7–20.5)	0.001

(Continued)

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TABLE 1 (Continued)

Variables	Development cohort							Validation cohort						
	All patients (*n* = 214)	3 months			6 months			All patients (*n* = 139)	3 months			6 months		
		Survivors (*n* = 192)	Non-survivors (*n* = 22)	*P*	Survivors (*n* = 184)	Non-survivors (*n* = 30)	*P*		Survivors (*n* = 123)	Non-survivors (*n* = 16)	*P*	Survivors (*n* = 115)	Non-survivors (*n* = 24)	*P*
Etiology (*n*, %)														
HBV	134 (62.6%)	119 (62.0%)	15 (68.2%)		112 (60.9%)	22 (73.3%)		84 (60.4%)	76 (61.8%)	8 (50.0%)		71 (61.7%)	13 (54.2%)	
HCV	7 (3.3%)	7 (3.6%)	0		7 (3.8%)	0		7 (5.0%)	6 (4.9%)	1 (6.3%)		6 (5.2%)	1 (4.2%)	
Alcoholism	5 (2.3%)	5 (2.6%)	0		5 (2.7%)	0		5 (3.6%)	5 (4.1%)	0		4 (3.5%)	1 (4.2%)	
Others	68 (31.8%)	61 (31.8%)	7 (31.8%)		60 (32.6%)	8 (26.7%)		43 (30.9%)	36 (29.3%)	7 (43.8%)		34 (29.6%)	9 (37.5%)	
Modes of decompensation (*n*, %)														
Ascites	181 (84.6%)	162 (84.4%)	19 (86.4%)		155 (84.2%)	26 (86.7%)		120 (86.3%)	105 (85.4%)	15 (93.8%)		99 (86.1%)	21 (87.5%)	
Variceal bleeding	69 (32.2%)	64 (33.3%)	5 (22.7%)		63 (34.2%)	6 (20.0%)		44 (31.7%)	39 (31.7%)	5 (31.3%)		36 (31.3%)	8 (33.3%)	
HE	9 (4.2%)	5 (2.6%)	4 (18.2%)		5 (2.7%)	4 (13.3%)		4 (2.9%)	1 (0.8%)	3 (18.8%)		1 (0.9%)	3 (12.5%)	
HRS	5 (2.3%)	1 (0.5%)	4 (18.2%)		0	5 (16.7%)		3 (2.2%)	0	3 (18.8%)		0	3 (12.5%)	

Data are expressed as number, mean ± standard deviation, median (25th–75th percentiles), or frequency [percentage (%)]. WBC, white blood cell; LYM, lymphocyte; HGB, hemoglobin; PLT, platelet; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ–glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; PT, prothrombin time; PNI, prognostic nutritional index; MELD, Model for End–Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome.

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TABLE 2 Comparison of clinical and laboratory characteristics between low and high PNI groups in the development and validation cohort in patients with decompensated liver cirrhosis.

Variables	Development cohort						Validation cohort					
	3 months			6 months			3 months			6 months		
	PNI < 35.47 (*n* = 122)	PNI > 35.47 (*n* = 92)	*P*	PNI < 35.47 (*n* = 122)	PNI > 35.47 (*n* = 92)	*P*	PNI < 35.47 (*n* = 79)	PNI > 35.47 (*n* = 60)	*P*	PNI < 35.47 (*n* = 79)	PNI > 35.47 (*n* = 60)	*P*
Gender (*n*, %)			0.196			0.196			0.861			0.861
Male	77 (63.1%)	50 (54.3%)		77 (63.1%)	50 (54.3%)		42 (53.2%)	31 (51.7%)		42 (53.2%)	31 (51.7%)	
Female	45 (36.9%)	42 (45.7%)		45 (36.9%)	42 (45.7%)		37 (46.8%)	29 (48.3%)		37 (46.8%)	29 (48.3%)	
Age (years)	61.0 ± 13.5	62.0 ± 12.1	0.578	61.0 ± 13.5	62.0 ± 12.1	0.578	62.6 ± 12.4	59.6 ± 12.7	0.164	62.6 ± 12.4	59.6 ± 12.7	0.164
WBC (10^9/L)	3.7 (2.4–5.5)	3.9 (2.7–5.3)	0.557	3.7 (2.4–5.5)	3.9 (2.7–5.3)	0.557	3.7 (2.4–5.8)	4.1 (3.1–6.2)	0.166	3.7 (2.4–5.8)	4.1 (3.1–6.2)	0.166
HGB (g/L)	91.7 ± 24.3	102.4 ± 25.5	0.002	91.7 ± 24.3	102.4 ± 25.5	0.002	87.9 ± 23.6	101.3 ± 30.8	0.004	87.9 ± 23.6	101.3 ± 30.8	0.004
PLT (10^9/L)	59.0 (41.0–92.5)	65.5 (48.3–108.3)	0.094	59.0 (41.0–92.5)	65.5 (48.3–108.3)	0.094	63.0 (44.0–98.0)	81.5 (52.0–116.8)	0.022	63.0 (44.0–98.0)	81.5 (52.0–116.8)	0.022
TBIL (μmol/L)	28.7 (18.1–48.3)	21.5 (15.0–33.4)	0.001	28.7 (18.1–48.3)	21.5 (15.0–33.4)	0.001	31.8 (19.8–54.8)	24.4 (15.0–37.8)	0.001	31.8 (19.8–54.8)	24.4 (15.0–37.8)	0.070
ALT (U/L)	25.0 (15.0–42.3)	25.0 (17.0–40.8)	0.917	25.0 (15.0–42.3)	25.0 (17.0–40.8)	0.917	23.0 (16.0–37.0)	24.0 (19.0–45.8)	0.279	23.0 (16.0–37.0)	24.0 (19.0–45.8)	0.279
AST (U/L)	37.0 (23.0–65.0)	31.0 (22.0–52.0)	0.094	37.0 (23.0–65.0)	31.0 (22.0–52.0)	0.094	37.0 (23.0–60.0)	34.5 (22.3–60.5)	0.975	37.0 (23.0–60.0)	34.5 (22.3–60.5)	0.975
GGT (U/L)	47.5 (19.8–155.3)	62.0 (28.5–140.8)	0.232	47.5 (19.8–155.3)	62.0 (28.5–140.8)	0.232	36.0 (18.0–83.0)	54.0 (24.5–150.8)	0.078	36.0 (18.0–83.0)	54.0 (24.5–150.8)	0.078
BUN (mmol/L)	6.0 (4.2–8.8)	5.2 (4.2–6.4)	0.060	6.0 (4.2–8.8)	5.2 (4.2–6.4)	0.060	6.9 (4.7–10.5)	5.8 (4.6–8.6)	0.044	6.9 (4.7–10.5)	5.8 (4.6–8.6)	0.044
Cr (umol/L)	69.8 (58.2–90.8)	64.6 (54.4–82.1)	0.061	69.8 (58.2–90.8)	64.6 (54.4–82.1)	0.061	60.7 (48.4–81.0)	57.4 (47.1–81.5)	0.230	60.7 (48.4–81.0)	57.4 (47.1–81.5)	0.230
PT (S)	15.5 (14.0–16.9)	13.7 (12.7–14.9)	<0.001	15.5 (14.0–16.9)	13.7 (12.7–14.9)	<0.001	15.6 (14.5–17.7)	14.2 (12.9–15.4)	< 0.001	15.6 (14.5–17.7)	14.2 (12.9–15.4)	<0.001
PNI	30.0 ± 3.7	40.6 ± 4.8	<0.001	30.0 ± 3.7	40.6 ± 4.8	<0.001	31.2 (27.9–33.0)	40.4 (37.4–43.8)	< 0.001	31.2 (27.9–33.0)	40.4 (37.4–43.8)	<0.001
MELD score	12.6 (10.2–16.0)	9.4 (8.1–11.4)	<0.001	12.6 (10.2–16.0)	9.4 (8.1–11.4)	<0.001	12.5 (10.0–16.3)	10.3 (8.3–12.6)	< 0.001	12.5 (10.0–16.3)	10.3 (8.3–12.6)	<0.001
Mortality (*n*, %)	20 (16.4%)	2 (2.2%)	0.001	27 (22.1%)	3 (3.3%)	<0.001	15 (19.0%)	1 (1.7%)	0.002	23 (29.1%)	1 (1.7%)	<0.001

Data are presented as number, mean ± standard deviation, median (25th–75th percentiles), or frequency [percentage (%)]. WBC, white blood cell; LYM, lymphocyte; HGB, hemoglobin; PLT, platelet; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ–glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; PT, prothrombin time; PNI, prognostic nutritional index; MELD, Model for End–Stage Liver Disease.

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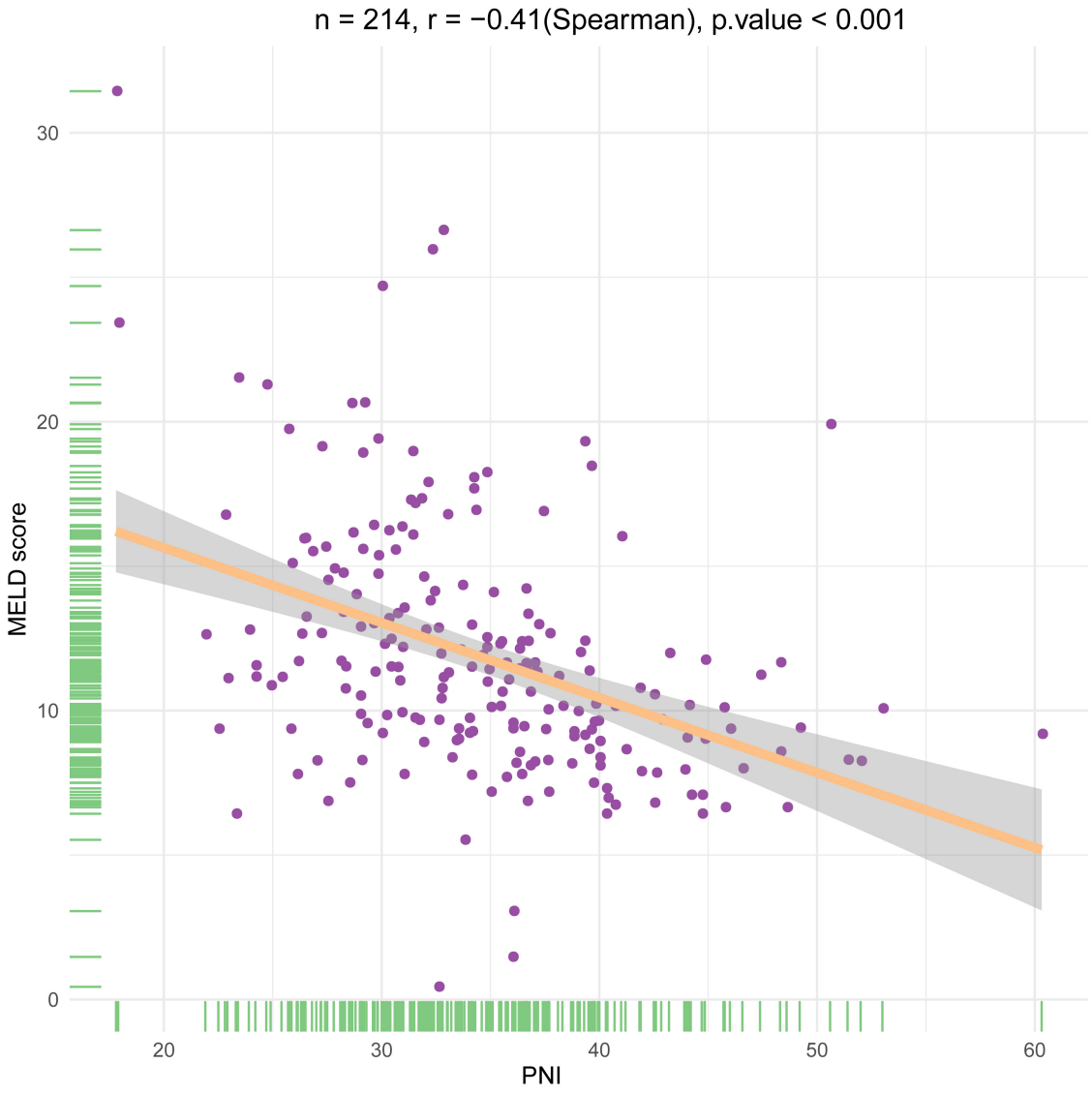

FIGURE 1
Scatter graphs illustrating the association between the prognostic nutritional index and the MELD score.

PNI is a simple index developed by Onodera et al., reflecting immune, inflammatory, and nutritional status (39). According to recent studies, PNI significantly correlates with adverse outcomes in various diseases (7–17). Zheng et al. reported that a lower PNI is an independent risk factor for higher mortality in patients with respectable esophageal squamous cell carcinoma (7). According to Chen et al., a lower PNI is independently correlated with increased cardiovascular disease death and overall mortality in patients with heart failure (11). Bodolea et al. found that a lower PNI is an independent predictor of higher mortality in patients with severe COVID-19 (17). Similarly, our results showed that a lower PNI is an independent predictor of poor prognosis in patients with DLC.

There are specific explanations as to why PNI can predict the prognosis in patients with DLC. Firstly, albumin can reflect systemic inflammation and nutritional status (40, 41). Serum albumin had a negative relationship with the intensity of the systemic inflammatory response (37, 38). It has been recognized to have a significant role in the pathogenesis of end-stage liver cirrhosis and is related to poor outcome (21–24). A recent study has also demonstrated that low serum albumin may be caused by a combination of hepatic reorganization of protein synthesis in the body and redistribution of albumin in and out of blood vessels under high inflammatory conditions (41). In patients with liver cirrhosis, although albumin levels are primarily influenced by hepatic synthetic function, it is also influenced by other factors such as decreased protein intake, increase of

TABLE 3 Factors correlated with 3-month, and 6-month mortality in multivariate analyses in patients with decompensated liver cirrhosis in the development cohort and validation cohort.

Variables	Development cohort				Validation cohort			
	3 months OR (95% CI)	*P*	6 months OR (95% CI)	*P*	3 months OR (95% CI)	*P*	6 months OR (95% CI)	*P*
WBC (10^9/L)	1.098 (0.935–1.280)	0.230	1.107 (0.957–1.279)	0.160	1.173 (0.951–1.469)	0.138	1.203 (0.994–1.486)	0.065
PLT (10^9/L)	1.005 (1.000–1.011)	0.044	1.005 (1.000–1.010)	0.072	1.005 (0.990–1.020)	0.469	0.999 (0.983–1.012)	0.837
AST (U/L)	1.002 (0.998–1.005)	0.349			0.990 (0.970–1.004)	0.238		
BUN (mmol/L)	1.086 (0.981–1.212)	0.122			1.087 (0.961–1.218)	0.160		
PT (S)	1.057 (0.843–1.329)	0.628	1.045 (0.868–1.261)	0.639	0.963 (0.757–1.152)	0.670	1.120 (0.945–1.408)	0.256
MELD score	1.059 (0.905–1.237)	0.469	1.076 (0.950–1.213)	0.232	1.167 (0.977–1.411)	0.095	1.057 (0.917–1.214)	0.430
PNI		0.037		0.006		0.036		0.006
Low	Reference		Reference		Reference		Reference	
High	0.187 (0.028–0.756)		0.162 (0.036–0.530)		0.098 (0.005–0.592)		0.053 (0.003–0.283)	

WBC, white blood cell; PLT, platelet; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; MELD, Model for End-Stage Liver Disease; PNI, prognostic nutritional index; OR, odds ratio; CI, confidence interval. Age, sex, hemoglobin, WBC, PLT, AST, BUN, PT, PNI, MELD score, total bilirubin, alanine aminotransferase, γ-glutamyl transpeptidase, and creatinine were included in the univariate logistic regression analysis. Variables that did not have a significant effect on mortality in the univariate logistic regression analysis were not included in the multivariate logistic regression analysis.

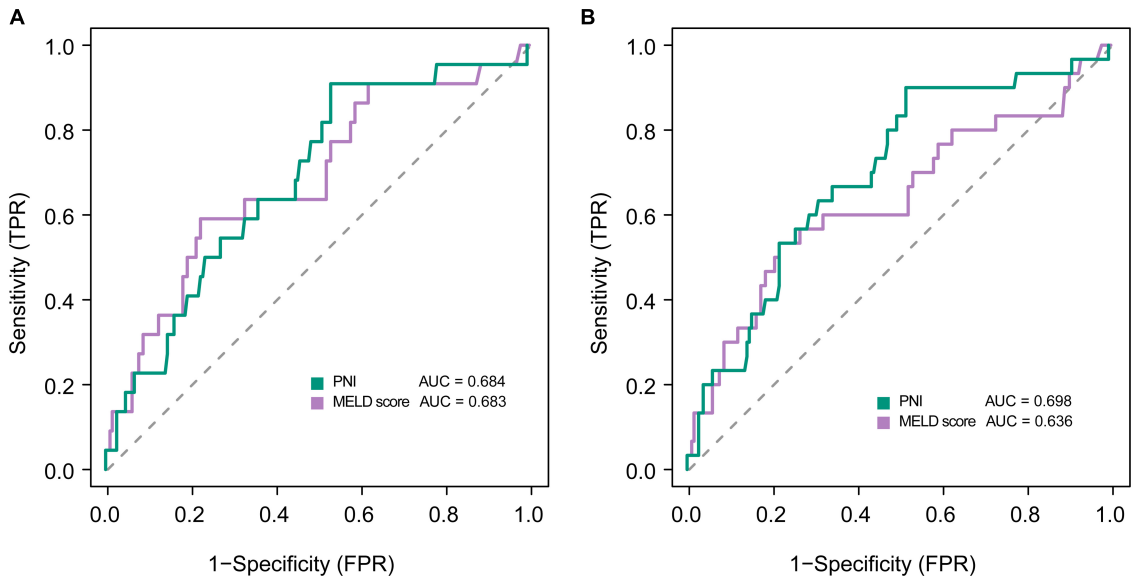

FIGURE 2
Receiver operating curves showing predictive accuracy of the MELD score and the PNI for mortality at **(A)** 3, and **(B)** 6 months in patients with decompensated liver cirrhosis.

the catabolic state, increased vascular permeability, systemic inflammatory response, protein-losing enteropathy secondary to portal hypertension, and impaired immunity (38, 40–48). Additionally, Topan et al. reported that low albumin levels were associated with malnutrition in patients with liver cirrhosis (49). Secondly, a previous study has shown that activated and differentiated CD4 + T lymphocytes are recruited to the inflamed liver and cause liver inflammation (50). Lymphopenia has been identified to be a marker of malnutrition and impaired immune response in patients with chronic liver disease (51, 52). Low lymphocytes were found to be associated with mortality in patients with advanced liver cirrhosis who were waiting for liver transplantation (53). Hence, the combination of lymphocytes and albumin primarily reflects inflammatory and immune status and partially reflects malnutrition that may help in predicting the prognosis of patients with DLC.

There are certain drawbacks in the current study. Firstly, it is a single-centered, retrospective, observational study, and selection bias cannot be avoided. Secondly, the predominant etiology of the patients in this study was hepatitis B virus

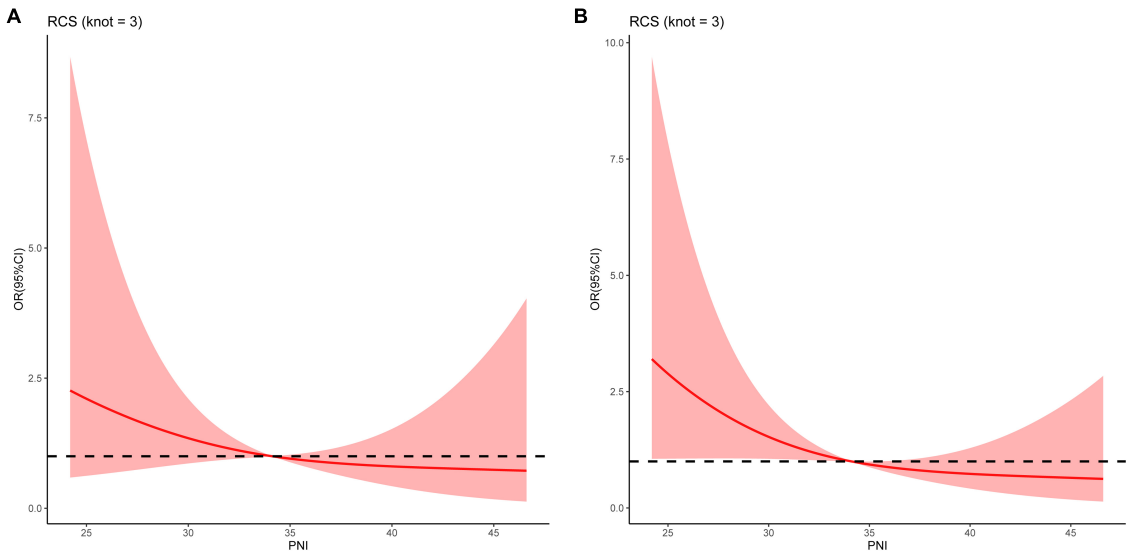

FIGURE 3
Restricted cubic spline curves for the relationships between the prognostic nutritional index and the risk of death at **(A)** 3, and **(B)** 6 months in patients with decompensated liver cirrhosis.

infection, requiring caution to extrapolate these findings to other populations, especially in western cirrhosis populations where alcohol and NASH predominate. Third, this study did not compare the predictive ability of PNI with other nutritional indicators, such as skeletal muscle index or phase angle markers, for the prognosis of patients with DLC. Hence, prospective multicentered research with large sample numbers is required to further evaluate the clinical relevance of the PNI in patients with DLC.

Conclusion

Prognostic nutritional index may be a potential and promising predictor of prognosis in patients with DLC. It is readily available and could be used to identify patients at high risk of death. This finding may be used to improve the prognosis in patients with DLC by adjusting the treatment strategies in clinical practice.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Scientific Research and New Technology Institutional Review Board of Yijishan Hospital of Wannan Medical College. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WW designed the research. YX and CH collected the data. YX and WW analyzed the data and wrote the main manuscript text. YX prepared all tables and figures. WW and CH revised the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1092059/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The flow chart of the patient selection process.

SUPPLEMENTARY FIGURE 2
The graphical presentation of the variables on admission. The units of variables were as follows: age, years; white blood cell (WBC), 10^9/L; lymphocyte (LYM), 10^9/L; hemoglobin (HGB), g/L; platelet (PLT), 10^9/L; albumin (ALB), g/L; total bilirubin (TBIL), μmol/L; alanine aminotransferase (ALT), U/L; aspartate aminotransferase (AST), U/L; γ−glutamyl transpeptidase (GGT), U/L; blood urea nitrogen (BUN), mmol/L; creatinine (Cr), μmol/L; prothrombin time (PT), s.

SUPPLEMENTARY FIGURE 3
Kaplan-Meier analysis curves for survival according to prognostic nutritional index levels in the development and validation cohort.

SUPPLEMENTARY FIGURE 4
Receiver operating curves of the MELD score, and the prognostic nutritional index for prediction of mortality in patients with decompensated liver cirrhosis in the validation cohort at **(A)** 3, and **(B)** 6 months.

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Role of perioperative nutritional status and enteral nutrition in predicting and preventing post-operative complications in patients with Crohn's disease

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Background: Perioperative immune-nutritional status is correlated with post-operative outcomes. This study aimed to evaluate whether pre-operative nutritional status could predict post-operative complications in patients with Crohn's disease (CD) and whether pre-operative enteral nutrition (EN) can prevent post-operative complications.

Methods: This retrospective cohort study analyzed the electronic health records of 173 patients diagnosed with CD in Ruijin Hospital, Shanghai, China, between August 2015 and May 2021: 122 patients had pre-operative nutritional support while 51 patients underwent surgery without pre-operative nutritional support. The pre-operative nutritional status, disease activity index, disease-related data, frequency of multiple surgery, operative data, and post-operative characters in each group were compared to determine whether the nutritional support and status could significantly affect post-operative outcome. One-to-one propensity score matching (PSM) was performed to limit demographic inequalities between the two groups.

Results: After PSM, no statistically significant differences were found in pre-operative patient basic characteristics between the two groups of 47 patients (98 patients in all) included in this study. Overall, 21 patients developed 26 post-operative complications. In terms of pre-operative nutritional status, the level of serum albumin (ALB), pre-albumin (pre-ALB), and hemoglobin (Hb) in the nutrition group were statistically higher than that in the control group. We also observed a statistically significant decrease in post-operative complications, need for emergency surgery, and staged operations, while the rate of laparoscopic surgery was higher in the nutrition group compared to the non-nutritional group. Post-operative complications were related to

pre-operative nutritional condition, which indicated that EN may improve the nutritional status and reduced the rate of post-operative complications.

Conclusion: Pre-operative nutritional status is correlated with post-operative outcomes while EN plays a positive role in preventing the post-operative complications. EN is useful for improving the pre-operative nutritional status and reducing the post-operative adverse events for CD patients undergoing surgery.

KEYWORDS

Crohn's disease, nutritional assessment, oral supplement, enteral nutrition, post-operative complications

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the intestinal mucosa which can occur discontinuously throughout the entire digestive tract. Its pathogenesis is still poorly understood (1, 2). In China, the morbidity and prevalence of CD are increasing constantly, which leads to a heavy economic and social burden (3). Although the innovation and application of series of new drugs has greatly improved the therapeutic effect (4), complications such as intestinal bleeding, obstruction, fistula, perforation, abscess still occur (5, 6), these patients as well as those who respond poorly to conservative treatment may require surgery (7, 8).

During the natural course of CD, the nutritional condition and the diet are important in the etiology of CD, particularly in regions where the rising prevalence rate has paralleled changes in eating habits and food industrialization (9, 10). High prevalence of malnutrition and micronutrient deficiencies were observed in patients with CD and constitutes a challenging issue for patients who require surgery (9). While malnutrition was confirmed to be an independent prognostic factor for increased risk of post-operative complications after abdominal surgery, which contributes to approximate 20–40% of surgical complication rates (11, 12). In this regards, early diagnosis of malnutrition is extremely important since pre-operative nutritional intervention may contribute to lower post-surgical complication and mortality rates (13–15). However, until now, there is few evidence directly linking nutritional status to post-operative complications in CD patients. Evidence that supports the effectiveness of nutritional support for patients with CD during peri-operative period, and whether it can contribute to lower post-operative complication incidence rate is scant (11, 16). Thus, we selected scored Patient-Generated Subjective Global Assessment (PG-SGA score) as a validated tool to screen patients' immune-nutritional status (17, 18), and we selected the comprehensive complication index (CCI) to quantify the post-operative complications within 30 days.

Furthermore, several strategies were adopted to establish a standard clinical protocol of pre-operative enteral nutrition (EN): including patient nutrition education programs, dietary instruction, partial enteral nutrition (PEN), exclusive enteral nutrition (EEN), and total parenteral nutrition (TPN), which can significantly reduce the effects of catabolism (19). Our primary hypothesis was that pre-operative EN would increase pre-operative immune-nutritional status and reduce 30-day post-operative complications, as measured using the CCI. The objective of this study is to evaluate whether the nutritional status could predict post-operative complications in CD patients and the benefit of EN on the nutritional status and preventing post-operative complications of CD patients.

2. Materials and methods

2.1. Study population

This retrospective study included all patients undergoing surgery for CD at Ruijin Hospital from 12 August 2015 to 19 May 2021. Included were patients with post-operative histological diagnosis of CD according to the European Crohn's and Colitis Organization (ECCO) guidelines (7, 8) and Consensus Opinion on Diagnosis and Treatment of inflammatory bowel disease (2018, Beijing) of the Chinese Inflammatory Bowel Disease Group (20), who underwent surgical resection due to failure of medical therapy or developed complications with the following inclusion criteria: (1) age $\geq$18 years, male or non-pregnant female; (2) American Society of Anesthesiologists (ASA) Grades I–III; and (3) complete follow-up data. All indications were discussed in the multidisciplinary team (MDT) conference including gastrointestinal surgeons, gastroenterologists, nutritionists, pathologists, radiologists, and nurses. Patients with incomplete clinical data or electronic health record were excluded. Patients

were divided into two groups according to whether they had received pre-operative nutritional support or not.

This study was approved by the hospital's Ethics Committee and all patients provided informed consent.

2.2. Nutritional assessment

All patients receiving nutritional support were assessed by the PG-SGA score and activity of CD with Crohn's Disease Activity Index (CDAI) before surgical procedure. The index was assessed by nutritionists and surgeons at the time of admission for surgery and were stored in patients' clinical database and electronic health record. Patients with CDAI scored 0 to 149 points were identified as remission, while patients with CDAI scored no less than 150 points were identified with active disease, according to the ECCO and Beijing guidelines (7, 8, 20). During the course of nutritional support, nutritional deficiency was screened by blood tests routinely, once every 3 months for patients with mild to severe active disease and once every 6 months in patients in asymptomatic remission. Laboratory data refer to the nutritional condition were collected from electronic health record.

2.3. Nutritional support

2.3.1. Protein

Protein requirements for patients in remission was 1 $g{\cdot}kg^{-1}{\cdot}day^{-1}$ in adults, similar to that recommended for the general population, while protein requirement was 1.2–1.5 $g{\cdot}kg^{-1}{\cdot}day^{-1}$ in adults with active disease (21). All patients were asked to adhere to nutrition education programs. The nutritionist provided individual dietetic recommendation for each patient (22).

2.3.2. Energy

Patients who could not meet the expected energy requirements underwent EN depending on the disease activity, duration of feeding, patient compliance, and gastrointestinal function. For the patients with asymptomatic remission, energy supply was 25–30 $kcal{\cdot}kg^{-1}{\cdot}day^{-1}$. PEN was recommended for these patients while 400–1800 $kcal{\cdot}d^{-1}$ through method of EN, the rest of energy requirement was taken by dietary. For patients with active disease, energy supply was 8–10% higher than the remission phase, which was 30–35 $kcal{\cdot}kg^{-1}{\cdot}day^{-1}$. For patients whose dietic intake did not meet the standard nutritional requirements, we selected EEN as the method of nutritional support. Patients who could not tolerate EN because of severe obstruction or fistule, TPN was recommended.

2.3.3. Microelement

The supplement of microelements was applied according to the result of laboratory blood test at the discretion of treating physician. Vitamin D and calcium supplements were recommended depending on the assessment of osteoporosis and level of serum calcium when 25-OH-Vit D was inferior to 75 nmol/L. Hypoferric anemia was corrected by iron therapy: oral supplement for the patients of mild iron deficiency anemia ($100\ g{\cdot}L^{-1} \leq hb < 120\ g{\cdot}L^{-1}$), intravenous iron supplementation for the patients of moderate anemia ($hb < 100\ g{\cdot}L^{-1}$). For the loss of vitamin B12, folic acid, potassium, magnesium, calcium, and phosphorus caused by diarrhea in CD patients, oral supplement was applicated according to the results of blood test.

2.4. Data collection

Laboratory data including white blood count (WBC), total lymphocyte count (TLC), red blood count (RBC), hemoglobin (Hb), albumin (ALB), pre-albumin (pre-ALB), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and parameter such as vitamin D, vitamin K, folic acid, 25-OH-Vit D, serum iron, serum calcium, serum phosphorus, serum magnesium. The prognostic nutritional index (PNI) was calculated from the serum ALB and TLC level, and the formula was PNI = 10 × ALB (g/dL) + 0.005 TLC (per mL).

Intraoperative data including surgical approach (open vs. laparoscopy), surgical option (resection or ostomy), surgical type, staged surgery or not, operation time, estimated blood loss (EBL) and intraoperative mortality or complication.

Post-operative data including post-operative complications recorded up to 30 days after surgery (graded according to the Clavien-Dindo classification), treatment of complications, time to bowel movements, post-operative fluid intake time, and length of stay (LOS) were obtained from electronic medical records. Time to bowel movements, post-operative fluid intake time, total LOS, post-operative LOS, and hospitalization expenses were recorded. CCI integrates all complications with their respective severities on a continuous scale ranging from 0 (no burden due to complications) to 100 (death as a result of complications). The CCI was scored by the CCI calculator available online.[1]

Baseline characteristics data including age, sex, ASA score, body mass index (BMI), comorbidity, smoking and alcohol history, medication history. perioperative data, and laboratory data were collected from the clinical database and electronic health record. CD-related data included CDAI,

1 http://www.assessurgery.com

PG-SGA score, Montreal classification, duration of disease, recurrence rate, and pre-operative drug therapy: either infliximab (documented dose of infliximab for more than 4 weeks before surgery) or corticosteroids (daily dose of 5 mg prednisolone or 4 mg methylprednisolone and within 4 weeks before surgical intervention). Missing data were treated with multiple imputations.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 26.0 (Armonk, NY, USA: IBM Corp). PSM analysis was conducted using a logistic regression model with the selected co-variates. We used a caliper width of 0.05 for the pooled standard deviation of the logit for PSM. Demographic and clinical characteristics were summarized and descriptively analyzed, and all quantitative values were presented as means and standard deviations. The Student's *t*-test or the Mann–Whitney *U*-test and Pearson's χ^2 (or Fisher's exact test) were used to compare continuous and categorical variables, respectively. All values were two tailed, and *p*-values < 0.05 were considered to be significant.

3. Results

3.1. Patient baseline characteristics

The study flow chart was summarized in Figure 1. We identified 183 consecutive cases of CD that underwent surgery from August 2015 to May 2021. We excluded 10 cases due to missing important records: missing nutritional support data ($n = 3$), missing nutritional assessment data ($n = 3$), and missing CCI report ($n = 4$). Hence, 122 cases in the nutrition group and 51 cases in the non-nutrition group were adjusted by PSM. Table 1 shows the baseline characteristics of the 173 patients. Compared with patients in the non-nutrition group, patients in nutrition group had younger ages ($p = 0.031$), higher ASA score ($p = 0.002$). The PSM analysis was conducted using a logistic regression model with the following co-variates: age, sex, ASA Score, and drug therapy (Table 1).

3.2. Patient demographics characteristics

After 1:1 PSM, there were 47 patients in each treatment strategy. No statistically significant difference was found in mean duration before surgery between the two groups ($p = 0.264$) (overall 65.35 ± 7.4 months). Ileal and ileocolonic involvement were the most common disease patterns, 34.0 and 33.0%, respectively. The overall recurrence rate was 24.5%, without any statistically significant difference between the two groups [10/47 (21.3%) vs. 13/47 (27.7%), $p = 0.472$]. Likewise, there were no statistically significant differences in age, gender, BMI, ASA score, duration from CD diagnosis to surgery, Montreal classification, and pre-operative medical history (Table 1).

3.3. Nutritional condition

The overall mean duration of nutritional treatment was 124 ± 22 days. All patients completed at least 3 months of nutritional support (range 93–475 days). Among all 47 patients who received nutritional support, 32 patients (68.1%) received PEN, 8 patients (17.0%) received EEN, 1 patient (2.1%) received EEN + PN, 6 patients (12.8%) received only dietary recommendation with micronutrient supplement. All 47 patients in the nutritional group demonstrated significant laboratory improvement of nutritional indices. Changes in inflammation and nutritional parameters are presented in Table 2. Mean-while, the nutritional group had a higher PG-SGA score, PG-SGA classification, CDAI index, and PNI ($p < 0.0001$). No statistically significant difference in BMI was observed (Table 3).

3.4. Operative data

The proportion of laparoscopic surgery and emergency surgery was statistically significantly higher in the nutritional support group: 91.5 vs. 40.4% ($p = 0.001$), 7.4 vs. 31.9% ($p < 0.0001$), respectively. Fewer patients received staged surgery in the nutritional group [5 (10.7%) vs. 18 (38.3%) ($p = 0.002$)]. The proportion of patients who had resections and/or protective diversion are indicated in Table 4.

3.5. Post-operative complications and perioperative characters

No data were missing for the primary endpoint (CCI), complications, LOS, or rate of re-operation. Data regarding post-operative outcomes are presented in Table 4. A lower 30-day CCI score of nutritional group was found in the primary outcome measure (2.86 vs. 9.89, $P = 0.015$). Post-operative complications developed in 21 (22.3%) patients, 6 (12.8%) in the nutritional group and 15 (31.9%) in the non-nutritional group ($p = 0.026$). A total of 26 complication events were observed while 5 (19.2%) events of Clavien-Dindo I complications, 3 (11.5%) events of Clavien-Dindo II complications, 12 (46.2%) events of Clavien-Dindo IIIa complications, 2 (7.7%) events of Clavien-Dindo IIIb complications, and 4 (15.4%) events of Clavien-Dindo IVa complications. The common complications

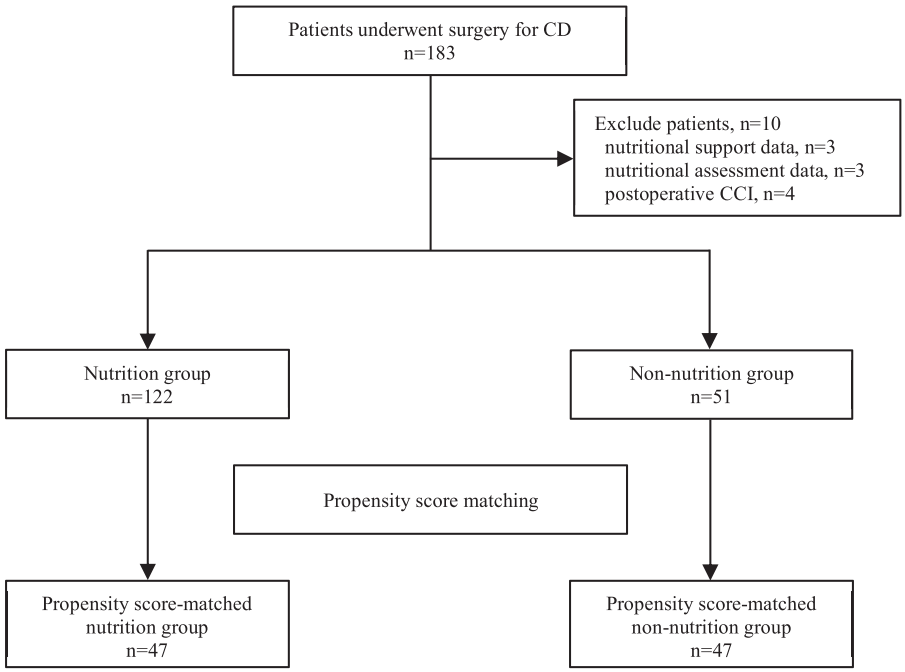

FIGURE 1
Study flow chat.

in our hospital were wound infection (19.2%), early post-operative bowel obstruction (19.2%), intra-abdominal abscess (19.2%), anastomotic leakage (11.5%), and excessive fluid losses of stoma (11.5%). Among all these post-operative complications, a lower incidence rate of intra-abdominal abscess (0 vs. 10.6%, P = 0.022) and excessive fluid losses of stoma (0 vs. 10.6%, P = 0.022) in nutritional group were mentioned. While no difference was observed between two groups of wound infection, early post-operative bowel obstruction, or anastomosis related complications (8.5 vs. 2.1%, P = 0.168, 6.4 vs. 8.5%, P = 0.694, 4.3 vs. 2.1%, P = 0.557, and 0.0 vs. 2.1%, P = 0.315, respectively) (Table 5). The number of multiple complication events for one patient in nutritional and non-nutritional group was 5 (10.6%) and 0 (0.0%), respectively (Table 5). Mean time of return of bowel movement, of total LOS, and of post-operative LOS were significantly fewer in the nutritional group with 2.94 ± 1.24 days, 14.62 ± 8.57 days, and 8.85 ± 6.04 days, vs. 3.67 ± 1.52 days, 20.62 ± 12.98 days, and 13.70 ± 9.90 days in the non-nutritional group (p = 0.013, 0.010, and 0.005, respectively) (Table 3).

4. Discussion

Despite the advent of medicine, a huge step forward for patients with CD, leading to a rapid response and huge remission of disease. However, complications such as intestinal bleeding, intestinal obstruction, fistula, perforation, abscess still exist (5–7). In such kind of occasion, surgery is still the recommended treatment (7). Therefore, it is crucial to enhance the outcome by optimizing perioperative management. Pre-operative malnutrition has been shown to be associated with increased risk of post-operative complications and increased LOS after abdominal surgery (12, 23, 24). Factors such as nausea, vomiting, abdominal pain, and diarrhea reducing oral food intake contribute to malnutrition in CD patients (25, 26). Furthermore, medications such as glucocorticoids often reduce phosphorus, zinc, and calcium absorption and may lead to osteoporosis (17). Although several studies demonstrated improved disease activity and prolonged time to relapse following nutritional support (27, 28), the efficacy and protocol of nutritional support has not been fully clarified.

Consistent with previous findings, pre-operative nutritional optimization was recommended in CD patients with poor nutritional status to minimize post-operative complications (23, 29). In our study, patients with lower nutritional status and higher inflammatory level are related with post-operative complications in quantity and severity. Furthermore, the pre-operative nutritional status may also have impact on post-operative recovery of gastrointestinal function. Prolonged post-operative ileus and delay in recovery of the gastrointestinal function were commonly observed in non-nutritional group, leading to a longer LOS directly. Meanwhile, malnutrition will also increase the rate of emergency surgery, staged surgery, and diversion. The difference of surgical strategy was done for the reason leading to the surgical difficulty such as severe

TABLE 1 Patient demographics characteristics.

	Before PSM		*P*-value	After PSM		*P*-value
	Nutrition	Non-nutrition		Nutrition	Non-nutrition	
No. of patients (%)	122 (70.5)	51 (29.5)		47 (50)	47 (50)	
Age (years)	37.9 ± 11.9	42.5 ± 14.5	**0.031**	39.8 ± 13.0	40.3 ± 12.5	0.865
Gender (%)			0.459			0.652
Male	79 (64.8)	36 (70.6)		34 (72.3)	32 (68.1)	
Female	43 (35.2)	15 (29.4)		13 (27.7)	15 (31.9)	
BMI	19.59 ± 3.32	20.01 ± 3.08	0.448	19.08 ± 3.43	20.01 ± 3.15	0.18
ASA score (%)			**0.002**			0.876
I/II	51 (41.8)	8 (15.7)		44 (93.6)	43 (91.5)	
III/IV	71 (58.2)	43 (84.3)		3 (6.4)	4 (8.5)	
Duration of disease (months)	63.59 ± 55.32	54.33 ± 65.90	0.414	75.70 ± 50.00	58.69 ± 67.48	0.264
Montreal classification						
Age (%)			0.067			0.816
A1	3 (0.6)	1 (1.7)		1 (2.1)	1 (2.1)	
A2	84 (48.6)	26 (15.0)		29 (61.7)	26 (55.3)	
A3	35 (20.2)	24 (13.9)		17 (36.2)	20 (42.6)	
Location (%)			0.083			0.161
L1	40 (23.1)	22 (12.7)		17 (36.2)	21 (44.7)	
L2	15 (8.7)	7 (4.0)		4 (8.5)	7 (14.9)	
L3	63 (36.4)	17 (9.8)		24 (51.1)	14 (29.8)	
L1 + L4	4 (2.9)	5 (2.3)		2 (4.3)	5 (10.6)	
B (%)			0.488			0.733
B1	2 (1.2)	1 (0.6)		2 (4.3)	1 (2.1)	
B2	69 (40.1)	24 (14.0)		24 (51.1)	22 (46.8)	
B3	50 (29.1)	26 (15.1)		21 (44.7)	24 (51.1)	
Drug therapy (%)			0.183			0.298
Monoclonal antibody	28 (16.2)	9 (5.2)		12 (25.5)	9 (19.1)	
Immunosuppressor	35 (20.2)	9 (5.2)		14 (29.8)	8 (17.0)	
5-ASA	28 (16.2)	11 (6.4)		11 (23.4)	11 (23.4)	
Steroids	9 (5.2)	5 (2.9)		3 (6.4)	5 (10.6)	
None	22 (12.7)	17 (9.8)		7 (14.9)	14 (29.8)	

The bold values represent $p < 0.05$.

intra-abdominal adhesions, tissue edema, complete intestinal obstruction, or severe fistula, which indicates that successful pre-operative nutritional support could decrease the occurrence of complications during the course CD and reduce intra-abdominal inflammation.

In recent studies, diet appears to play an important role in disease pathogenesis (23, 24, 30, 31). Recent studies have shown that EEN can induce remission and mucosal healing (32, 33). So far, nutritional support, including dietary and EN is likely to play an important role during the treatment of CD. But few evidence support the effectiveness of EN. Furthermore, the evidence to support the interplay between nutritional status and post-operative complications is still lacking. Based on our results, a specific nutritional strategy may be able to play a pivotal role in improving immune-nutritional status and preventing post-operative complications of CD patients. The pre-operative EN was found to significantly improve the nutritional status scored by PG-SGA assessment and reduce the inflammatory response according to CDAI score. Meanwhile, improvements in level of serum albumin concentration, pre-albumin concentration, and TLC were also mentioned. The TLC indicates the immunological status of patient, which is also one

TABLE 2 Laboratorial inflammation and nutritional parameters.

Blood test	Nutrition (n = 47)	Non-nutrition (n = 47)	P-value
WBC, $\times 10^9$/L, mean (SD)	5.45 (± 2.45)	7.93 (± 5.25)	**0.004**
TCL, $\times 10^9$/L, mean (SD)	1.33 (± 0.55)	1.03 (± 0.78)	**0.035**
CRP, mg/L, mean (SD)	4.00 (1.05–10.50)	21.75 (1.00–52.25)	**0.014**
PNI	43.84 (± 7.70)	36.70 (± 7.99)	**0.000**
ESR, mm/60 min, mean (SD)	12.46 (± 2.27)	19.50 (± 4.21)	0.113
Pre-ALB, mg/L, mean (SD)	218.28 (± 73.16)	160.96 (± 69.51)	**0.000**
Alb, g/L, mean (SD)	37.32 (± 7.74)	31.66 (± 6.87)	**0.000**
Hb, g/L, mean (SD)	118.98 (± 24.56)	112.73 (± 26.03)	0.248
Fe, mmol/L, mean (SD)	10.84 (± 6.43)	9.07 (± 5.06)	0.442
Ca, mmol/L, median (range)	2.27 (± 0.27)	2.11 (± 0.16)	**0.001**
P, mmol/L, median (range)	1.25 (± 0.25)	1.12 (± 0.42)	0.083
Mg, mmol/L, mean (SD)	0.83 (± 0.07)	0.83 (± 0.05)	0.962
Folate, nmol/L, mean (SD)	19.25 (± 5.63)	12.02 (± 8.22)	**0.026**
Ferritin, ng/ml, mean (SD)	182.72 (± 75.72)	129.69 (± 49.17)	0.572
25-OH-D, ng/ml, mean (SD)	49.60 (± 20.75)	31.02 (± 11.65)	**0.024**

The bold values represent $p < 0.05$.

TABLE 3 Nutritional condition.

Nutritional status	Nutrition (n = 47)	Non-nutrition (n = 47)	P-value
BMI, kg/m^2, mean (SD)	20.01 (± 3.15)	19.09 (± 3.43)	0.180
CDAI, mean (SD)	229.70 (± 86.43)	386.60 (± 44.16)	**0.001**
PG-SGA, mean (SD)	5.51 (± 4.41)	9.34 (± 4.11)	**0.000**
PG-SGA Classification, n (%)			**0.000**
A	5 (10.6)	1 (2.1)	
B	36 (76.6)	20 (42.6)	
C	6 (12.8)	26 (55.3)	
Duration of nutritional treatment, days, mean (SD)	124 (± 22)	/	
PEN, n (%)	32 (68.1%)	/	
EEN, n (%)	8 (17.0%)	/	
EEN + PN, n (%)	1 (2.1%)	/	
Micronutrient supplement only, n (%)	6 (12.8%)	/	
Post-operative ileus recovery, days, mean (SD)	2.9 (± 1.2)	3.7 (± 1.5)	0.013
Time to liquid food, days, median (range)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.309
LOS, days, mean (SD)	20.6 (± 13.0)	14.6 (± 8.6)	**0.010**
Post-operative LOS, days, mean (SD)	8.9 (± 6.0)	13.7 (± 9.9)	**0.005**

The bold values represent $p < 0.05$.

of the important components of PNI score. Various studies have indicated that T lymphocytes affected by the systemic inflammatory response play an important role in the depression of innate cellular immunity of intestinal inflammation in cancer patients and found PNI an independent prognostic indicator in predicting post-operative complication (34, 35). Accompany with the significant decrease of inflammatory indicators such as WBC and CRP, our results indicated the beneficial effect of this new kind of comprehensive nutritional strategy in alleviating nutritional status and intestinal inflammation in CD patients.

Micronutrient status is also impacted by inflammatory severity and disease location, which may reduce surface

TABLE 4 Operative data.

Surgical index	ALL (*n* = 94)	Nutrition (*n* = 47)	Non-nutrition (*n* = 47)	*P*-value
Surgical approach, *n* (%)				**0.000**
Laparoscopy	62 (66.0)	43 (91.5)	19 (40.4)	
Laparotomy	32 (34.0)	4 (8.5)	28 (59.6)	
Type of surgery, *n* (%)				**0.000**
Emergency surgery	57 (60.6)	17 (18.1)	40 (42.6)	
Elective surgery	37 (39.4)	30 (31.9)	7 (7.4)	
Non-stage surgery, *n* (%)	71 (75.5)	42 (89.3)	29 (61.7)	**0.002**
Staged surgery, *n* (%)	23 (24.5)	5 (10.7)	18 (38.3)	
Diversion, *n* (%)	25 (26.6)	19 (40.4)	6 (12.8)	**0.002**

The bold values represent $p < 0.05$.

TABLE 5 Post-operative complications and perioperative characters.

Post-operative outcome	Nutrition (*n* = 47)	Non-nutrition (*n* = 47)	*P*-value
CCI			
Mean (SD)	2.86 (± 1.15)	9.89 (± 2.31)	**0.008**
Median (IQR)	0 (0–19.96)	0 (0–2.42)	**0.015**
Post-operative complications, *n* (%)	6 (12.8)	15 (31.9)	**0.026**
Clavien-Dindo classification, *n* (%)			0.198
I	1 (2.1)	4 (8.5)	
II	1 (2.1)	2 (4.3)	
III	6 (12.8)	8 (17.0)	
IV	0 (0.0)	4 (15.4%)	
Wound infection, *n* (%)	4 (8.5)	1 (2.1)	0.168
Early post-operative bowel obstruction, *n* (%)	3 (6.4)	4 (8.5)	0.694
Intra-abdominal abscess, *n* (%)	0 (0.0)	5 (10.6)	**0.022**
Anastomotic leakage, *n* (%)	2 (4.3)	1 (2.1)	0.557
Anastomotic bleeding, *n* (%)	0 (0.0)	1 (2.1)	0.315
Excessive fluid losses of stoma	0 (0.0)	5 (10.6)	**0.022**
1 issue of post-operative complications	6 (12.8)	10 (21.3)	**0.029**
≥2 issue of post-operative complications	0 (0.0)	5 (10.6)	**0.029**

The bold values represent $p < 0.05$.

area for absorption (36). The level of serum microelement may also be affected by some medicines (36). Weisshof et al. indicated that these micronutrients lead to deleterious downstream effects such as impaired immune response within the gut, and inflammation because of increased production of reactive oxygen species (37). In this study, we monitored important nutrients such as folate, 25-OH-vit D, calcium, potassium, magnesium, and phosphorus which were determined to be frequently suboptimal in patient with CD (38, 39). The statistic between two groups indicated that micronutrients supplementary play an important role in treatment of CD patients whose micronutrient intake from dietary was suboptimal.

This study is, to the best of our knowledge, the first study focusing on the application of EN on post-operative outcomes of CD patients. We used PSM for potential imbalances between groups, which confirmed the robustness of our conclusions. On account of CCI, we can quantify the post-operative complication more precisely with the application of such a comprehensive and sensitive measure. Regular follow-up consultation no longer than 3 or 6 months and weekly self-reporting was executed in our program since compliance is often limited for the strategy

of dietary, EEN, PEN. In light of these design considerations, we believe that our results contribute new evidence for the role of nutritional support in CD patients who are candidates for surgical treatment.

Our result should be considered with some limitations. Groups were not balanced at baseline for age and ASA scores at first, however, our analyses were adjusted for these potential confounders. There was a considerable rate of missing data for PG-SGA score, CDAI index as a result of missing follow-up consultations. These missing data were handled with multiple imputation to reduce the risk of attrition bias. And the self-reporting database such as dietary compliance might be subject to reporting bias. Last but not least, this is a retrospective observational study which outcomes might be influenced by our local experience, a multi-center prospective study is excepted.

5. Conclusion

In conclusion, pre-operative nutritional status is correlated with post-operative outcomes while EN plays a positive role in preventing the post-operative complications. EN is a useful method for improving the pre-operative nutritional status and reducing the post-operative adverse events for CD patients undergoing surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Ruijin Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZH, TJ, YJ, and QJ: conceptualization. TJ, YJ, and QJ: writing—original draft. ZH, MZ, AF, and YS: review and editing. SX: supervision. All authors read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The influence of the China GLIM standards on the diagnosis of malnutrition in patients with hematopoietic stem cell transplant

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Background: The muscle-related indicator is removed from Global Leadership Initiative on Malnutrition (GLIM) criteria implemented in China for many reasons. Patients with hematopoietic stem cell transplants are at nutrition risk and can enter into the second step of GLIM; thus, they are suitable for learning the diagnosing malnutrition significance between primary GLIM and GLIM-China criteria. This article aims to explore the role of muscle mass in the diagnostic criteria of malnutrition and the effects of GLIM-China for diagnosing malnutrition.

Methods: A total of 98 inpatients with hematopoietic stem cell transplants (HSCT) were recruited. Nutrition risk was assessed by using the Nutritional Risk Screening 2002 (NRS-2002). Appendicular skeletal muscle mass (ASMI) and fat-free mass index (FFMI) were determined using the bioelectrical impedance analysis (BIA) method. Malnutrition is defined by GLIM-China, GLIM, and PG-SGA. We use erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to assess inflammation in GLIM and GLIM-China. The correlation or consistency among ASMI, FFMI, ESR, CRP, GLIM-China, GLIM, and PG-SGA was evaluated, respectively.

Results: One hundred percent instead of the patients had nutritional risk. The magnitude of malnutrition using PG-SGA, GLIM, and GLIM-China was 75.5, 80.6, and 64.3%, respectively. GLIM-China and PG-SGA showed the same performance ($p = 0.052$ vs. 1.00) and agreement (kappa = 0.404 vs. 0.433, $p < 0.0001$) with the FFMI. Consistency was noted between ASMI and PG-SGA in the assessment of malnutrition ($p = 0.664$) with a good agreement (kappa = 0.562, $p = 0.084$). ASMI and FFMI could determine muscle mass reduction, which could not be determined by BMI, albumin (ALB), and pre-albumin (pre-ALB); 34% of GLIM-China (−) patients were with low ASMI, and 40% with low FFMI; 30.0% of patients with PG-SGA (<4) still have low ASMI, and 38.2% have low FFMI.

Conclusion: If only the PG-SGA scale is used as a diagnostic criterion for evaluating malnutrition, a large proportion of patients with reduced muscle mass will be missed, but more patients with muscle loss will be missed *via* GLIM-China. Muscle-related indicators will help diagnose malnutrition.

KEYWORDS

muscle mass, HSCT, malnutrition, GLIM-China, PG-SGA

1. Background

Malnutrition assessment is quite important for patients with potential nutritional risks. In 2018, muscle mass reduction was included in the Global Leadership Initiative on Malnutrition (GLIM) criteria as a diagnostic criterion. A two-step approach for the malnutrition diagnosis was selected: first, screening to identify nutrition risk status by the use of certain validated screening tools such as Nutrition Risk Screening 2002 (NRS-2002), which is based on evidence-based medicine, and second, evaluating to diagnose and alleviating the severity of malnutrition (1).

Unfortunately, it is difficult to routinely measure muscle mass due to the limitations of measurement methods in clinical work, and it is also controversial to confirm the cutoff value of muscle mass loss in the Chinese people due to the lack of evidence (2). Many researchers have tried to use the calf circumference or fat-free mass index (FFMI) tested by bioelectrical impedance analysis (BIA) as a muscle mass indicator (3), which has not yet been widely recognized. In addition, it has been suggested that muscle mass-related indicators should be removed from the phenotypic criteria by the Chinese Nutrition Screening–Undernutrition–Support–Outcome–Cost/effective (NUSOC) Group. Thus, we will refer to it as the GLIM-China criteria in the following text (2, 4, 5). Herein, we explore whether there is a difference between GLIM-China and primary GLIM in diagnosing malnutrition. All patients with hematopoietic stem cell transplant (HSCT) could enter step 2 of GLIM if they have an NRS-2002 score of 3 at least in the peri-transplant period, who are considered the target population of this study.

Before the GLIM, there were many classic criteria for diagnosing malnutrition. ESPEN recommended a body mass index (BMI) <18.5 kg/m^2 to define malnutrition, or the combined finding of unintentional weight loss (mandatory) (weight loss $>10\%$ indefinite of time, or $>5\%$ over the last 3 months) and either a reduced BMI or a low FFMI (6). While PG-SGA is the most widely used malnutrition assessment tool for patients with cancer (7, 8), no objective and accurate data related to muscle mass are included (9).

This study aims to objectively compare the differences among muscle indicators and GLIM-China, GLIM, PG-SGA, BMI, and albumin (ALB) in the diagnosis of malnutrition, illustrating that muscle mass measurement may help diagnose malnourished patients with HSCT who are neglected by malnutrition assessment tools.

2. Materials and methods

2.1. Subjects

A total of 98 inpatients with HSCT in the hematology department were recruited from 2019 to 2020. Inclusion criteria were as follows: age $\geq$10 and $<$60 y and patients who met the hematopoietic stem cell transplantation criteria according to the evaluation of doctors in the hematology department. Exclusion criteria were as follows: pregnant and lactating patients; patients with severe infection or severe heart, liver, and kidney dysfunction; and patients with HSCT who did not agree to participate in this study.

2.2. Methods

Enrolled patients underwent blood sampling, body composition test, nutrition risk screening, and malnutrition diagnosis under fasting conditions under the guidance of a nutritionist. The methods are given in detail in the following paragraphs.

2.2.1. Blood collection and analysis protocol

Fasting blood was collected for the measurement of albumin (ALB), ESR, and CRP. All samples were analyzed using the same reagent lot. CRP was determined by immunoturbidimetry (Beckman Image 800), and ESR was tested using the microcapillary method (ALIFAX TEST1). ALB and pre-ALB were tested by using the bromocresol green method (Hitachi, Japan).

2.2.2. Body composition analysis

The body composition of recruited patients was measured by using the BIA method. The appendicular skeletal muscle mass

(ASMI), fat-free mass index (FFMI), etc. were determined using the Biospace Inbody S10 composition analyzer (Biospace Co., Ltd., Seoul, Korea). ASMI measurements $\leq$7 kg/m^2 for men or $\leq$5.7 kg/m^2 for women were defined as low ASMI. An FFMI $<$17 kg/m^2 for men or $<$15 kg/m^2 for women was defined as low FFMI (10). Height and body weight were measured without shoes and under fasting, and then the body mass index (BMI) was calculated. A BMI of $<$18.5 kg/m^2 was defined as a low BMI.

2.2.3. Nutrition risk screening and malnutrition diagnosis

The NRS-2002 was used for the screening of nutrition risk, and an NRS-2002 score of $\geq$3 was suggestive of nutrition risk [NRS-2002 (+)]. Nutritional assessment was carried out using the PG-SGA scale, and a PG-SGA score of $\geq$4 was defined as malnutrition (9, 11).

The GLIM criteria, a two-step model for malnutrition diagnosis, containing screening and assessment, were used in our study. The primary GLIM criteria contain phenotypic (three components) and etiologic (two components) parts (12). Fulfilling at least one component in each part is necessary to diagnose malnutrition. In the phenotypic criteria, a weight loss of $>$5% within the past 6 months was considered positive. In Chinese patients, a BMI of $<$18.5 kg/m^2 was considered low BMI if a patient was aged $<$70 years. Muscle mass reduction is excluded from the GLIM criteria mentioned earlier according to GLIM-China (2, 4, 5, 13).

2.2.4. Statistical analysis

Statistical analysis was carried out by using SPSS version 26, and data were subjected to normal distribution analysis. Data with a normal distribution (weight, BMI, FFMI, ASMI, phase angle, BFP, BCM, and BMR) are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and were compared using the *t*-test. Data with a non-normal distribution (height, age, ALB, pre-ALB, VFA, CRP, ESR, NRS-2002, PG-SGA, and GLIM-China) are expressed as M+QR and were compared using the Wilcoxon rank sum test. McNemer and consistency tests were also used to examine the consistency of muscle mass indicators (ASMI and FFMI) using malnutrition diagnostic tools (GLIM-China, PG-SGA, and BMI) and biological markers (ALB and pre-ALB), respectively. The correlation among FFMI, ASMI, PG-SGA, GLIM-China, ASMI, FFMI, and CRP in the identification of malnutrition criteria of ESPEN 2015 was evaluated by using Spearman rank correlations; the relationship among ESR, CRP, PG-SGA, and GLIM-China was assessed by using logistic regression. A *P*-value of $<$0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

According to the NRS-2002, all patients with HSCT were at nutrition risk. According to PG-SGA, patients with scores of 2–3 were 24.5%, and those with scores $\geq$4 were 75.5%. The magnitude of malnutrition using PG-SGA, GLIM, and GLIM-China was 75.5%, 80.6%, and 64.3%, respectively (Table 1). In total, 58.16% of patients had low ASMI, 79.6% of patients had a low FFMI, 10.2% of patients had a BMI $<$18.5 kg/m^2, 16.3% of patients had ALB levels lower than 35 g/L, and 35.5% of patients had pre-ALB levels lower than 200 mg/L.

3.2. Body composition and biochemical indexes in patients with different characteristics

Appendicular skeletal muscle mass and FFMI in male patients were significantly higher than those in female patients ($p < 0.0001$). ASMI and FFMI were similar among patients treated with allo-HSCT and auto-transplantation and were not significantly different between groups with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), multiple myeloma (MM), and other diseases (Table 2).

Female patients had lower pre-albumin ($p < 0.0001$) and albumin concentrations than male patients ($p = 0.0054$), but there was no significant difference in CRP and ESR between the male and female patients. The pre-albumin of patients with autologous stem cell transplant was higher than that of patients with allogeneic hematopoietic stem cell transplantation ($p = 0.0362$). No significant difference was found in ALB, CRP, and ESR levels between the two transplantation methods. Patients with AML had higher pre-albumin concentrations than patients with MM ($p = 0.0088$), and patients with AML had higher albumin concentrations than patients with MM ($p = 0.0244$) (Table 3).

3.3. ASMI and FFMI were consistent in malnutrition assessment using diagnostic tools of PG-SGA and GLIM-China

According to McNemer and consistency tests, inconsistent results were noted between FFMI and BMI in the assessment of malnutrition ($p < 0.001$), and there was little agreement between the FFMI and BMI (kappa = 0.274, $p < 0.0001$). FFMI and ALB were inconsistent in the assessment of malnutrition ($p < 0.0001$), with a poor agreement (kappa = 0.12, $p = 0.094$). FFMI and pre-ALB were also inconsistent in the assessment of nutritional status ($p <0.001$), with a similar poor agreement

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TABLE 1 Nutritional status and human body composition of patients with peri-HSCT.

Parameters	$\bar{x}+s/M+QR$
Height (m)	1.62 ± 7.82
Weight (kg)	53.40 ± 13.95
BMI (kg/m^2)	21.35 ± 5.00
Age	39.14 ± 14.97
Gender	
Male	54 (55.1%)
Methods	
Allo-HSCT	66 (67.3%)
Autotransplantation	32 (32.7%)
Disease	
AML	34 (34.7%)
ALL	14 (14.3%)
MM	30 (30.6%)
Others (NHL, CML etc.)	20 (20.4%)
NRS-2002 score	
3	43 (43.9%)
4	12 (12.2%)
5	7 (7.1%)
6	36 (36.8%)
PG-SGA score	
2–3	24 (24.5%)
4–8	24 (24.5%)
≥9	50 (51.0%)
GLIM	
Positive	79 (80.6%)
Negative	19 (19.4%)
GLIM-China	
Positive	63 (64.3%)
Negative	35 (35.7%)
Body composition	
ASMI (kg/m^2)	6.23 ± 1.26
FFMI (kg/m^2)	15.36 ± 2.35
BFM (kg)	13.3 ± 6.02
BFP (%)	23.9 ± 8.71
BCM (kg)	26.10 ± 5.69
VFA (cm^2)	63.20 ± 33.00
BMR (kcal)	1,248.3 ± 180.0
Body phase angle	4.55 ± 0.876
Biochemical values	
ALB (g/L)	16.96 ± 33.40
pre-ALB (mg/L)	215.40 ± 77.00
CRP (mg/L)	4.12 ± 10.76
ESR (mm/h)	31.50 ± 31.50

ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index; BFM, body fat mass; BFP, body fat percent; VFA, visceral fat area; BCM, body cell mass; BMR, basal metabolic rate; NHL, non-Hodgkin's lymphoma; CML, chronic myeloid leukemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ALB, albumin.

TABLE 2 Human body composition in patients with different characteristics.

Variables	ASMI (kg/m^2)	FFMI (kg/m^2)
Gender		
M	6.89 ± 1.15	16.16 ± 2.40
F	5.42 ± 0.87****	14.23 ± 1.69****
Methods		
Allo-HSCT	6.14 ± 1.04	15.28 ± 1.81
Auto-transplantation	6.63 ± 1.51	16.14 ± 2.79
Disease		
AML	6.45 ± 0.25	15.45 ± 0.43
ALL	5.84 ± 0.28	14.18 ± 0.52
MM	6.14 ± 0.20	15.27 ± 0.34
Others (CML, NHL etc.)	6.28 ± 0.30	15.47 ± 0.50

****$p < 0.0001$, female vs. male patients.

(kappa = 0.122, $p = 0.168$). Interestingly, the results were consistent between FFMI and GLIM-China in the assessment of malnutrition ($p = 0.052$), with a moderate agreement (kappa = 0.404, $p < 0.0001$). The positive rate determined by FFMI (66.3%) was higher than that by GLIM-China (64.3%); thus, there was a trend toward significantly different results. We also found consistent results between FFMI and PG-SGA in the assessment of malnutrition ($p = 1.00$), with a fair agreement (kappa = 0.433, $p < 0.0001$). The positive rate determined by FFMI (66.3%) was slightly higher than that by PG-SGA (65.3%), but no significant difference was found (Table 4).

Inconsistency was noted between ASMI and BMI in the assessment of malnutrition ($p < 0.001$), and there was low agreement (kappa = 0.337, $p < 0.001$), comparing ASMI instead with ALB and pre-ALB, we also found no consistency between ASMI and ALB ($p < 0.001$; kappa = 0.228, $p = 0.004$), and ASMI and pre-ALB ($p = 0.002$; kappa = 0.173, $p = 0.066$). Significant consistency was noted between ASMI and PG-SGA in the assessment of malnutrition ($p = 0.664$), and there was good agreement between ASMI and PG-SGA (kappa =

TABLE 3 Serum biomarkers in patients with different characteristics.

Variables	ALB (g/L)	pre-ALB (mg/L)	CRP (mg/L)	ESR (mm/h)
Gender				
M	39.50 ± 4.12	224.95 ± 67.84	7.00 ± 9.16	33.09 ± 26.76
F	37.04 ± 4.41**	191.29 ± 45.72****	12.82 ± 19.23	36.02 ± 22.12
Methods				
Allo-HSCT	37.56 ± 3.39	202.03 ± 39.81	9.39 ± 17.62	35.78 ± 22.34
Autotransplantation	40.86 ± 4.26	228.72 ± 78.14	5.74 ± 13.62	21.47 ± 18.04
Disease				
AML	40.14 ± 0.87	237.2 ± 10.10	10.03 ± 2.67	32.29 ± 4.16
ALL	36.09 ± 1.15	245.5 ± 31.90	7.29 ± 2.34	28.08 ± 6.59
MM	37.61 ± 0.63	202.3 ± 7.65	9.19 ± 3.31	34.97 ± 4.12
Others (CML, NHL etc.)	38.23 ± 0.81[ab]**	209.7 ± 12.14[c]**	11.81 ± 2.97	41.20 ± 6.52

**$p = 0.0054$ female vs. male patients; ****$p < 0.0001$, female vs. male patients.
[a]$p = 0.0118$, AML vs. ALL.
[b]$p = 0.0244$, AML vs. MM.
[c]$p = 0.0088$, AML vs. MM.

0.562, $p < 0.0001$). The positive rate determined by ASMI (58.2%) was slightly lower than that by PG-SGA (60.6%), but these results were not significantly different. Consistency was found between ASMI and GLIM-China in the assessment of malnutrition ($p = 0.362$), with a poor agreement (kappa = 0.358, $p < 0.001$), and the positive rate determined by ASMI (58.2%) was lower than that by GLIM-China (64.3%, $p < 0.001$) (Table 4).

3.4. Correlations of body composition with PG-SGA and GLIM-China

Further correlation analyses revealed a moderate negative relationship between FFMI and PG-SGA ($r_s = -0.513$, $p < 0.0001$). This negative relationship was noted in both male ($r_s = -0.204$, $p = 0.142$) and female patients ($r_s = -0.4956$, $p = 0.001$). A negative relationship was noted between ASMI and PG-SGA ($r_s = -0.480$, $p < 0.0001$), and this negative relationship was present in both male ($r_s = -0.247$, $p = 0.075$) and female patients ($r_s = -0.515$, $p < 0.0001$). There was also a negative relationship between FFMI and GLIM-China ($r_s = -0.480$ $p < 0.0001$) and present in male patients ($r_s = -0.115$ $p = 0.411$) but not in female patients ($r_s = -0.519$, $p < 0.0001$). A negative relationship between ASMI and GLIM-China ($r_s = -0.372$, $p < 0.0001$) and present in male patients ($r_s = -0.139$, $p = 0.322$) but not in female patients ($r_s = -0.439$, $p = 0.003$).

3.5. Correlation between biochemical criteria (ESR and CRP) and GLIM-China, PG-SGA

We used logistic regression to evaluate the effect of ESR and CRP on the diagnosis of malnutrition in GLIM-China. The result of the logistic regression model was statistically significant [$\chi^2_{(4)} = 6.487$, $p < 0.05$] as the model explained 8.9% of the variation (Nagelkerke R2) with or without malnutrition and was able to correctly classify 65.6% of the patients. The sensitivity of the model was 91.8%, the specificity was 20.0%, the positive predictive value was 65.3%, and the negative predictive value was 56.8%. Equally, the logistic regression model of ESR, CRP, and PG-SGA was statistically significant [Table 5; $\chi^2_{(4)} = 11.407$, $p = 0.003$], and this model explained 16.8% of the variation (Nagelkerke R2) with or without malnutrition and was able to correctly classify 76% of patients. The sensitivity of this model was 100%, the specificity was 0.00%, the positive predictive value was 74.5%, and the negative predictive value was 0.00%.

Taken together, ESR and CRP had higher sensitivity to malnutrition than GLIM-China and PG-SGA, but the specificity was low, and the prediction of PG-SGA for malnutrition was better. Compared with PG-SGA, the false-negative rate of ESR and CRP was lower, and the false-positive rate was similar to that of GLIM-China.

4. Discussion

During hematopoietic stem cell transplantation, abnormal taste, poor appetite, and impaired digestion, as well as a

TABLE 4 Consistence of ASMI and FFMI with nutritional scales/parameters in the nutritional assessment.

BIA	ALB		Pre-ALB (93, missing = 5)		BMI		PG-SGA		GLIM-China		Total
	+	−	+	−	<18.5	≥18.5	<4	≥4	+	−	
Low ASMI	20 (83.3)	37 (50.0)	23 (69.7)	30 (50.0)	24 (92.3)	33 (45.8)	48 (70.6)	9 (30.0)	45 (71.4)	12 (34.3)	57 (58.2)
Normal ASMI	4 (16.7)	37 (50.0)	10 (30.0)	30 (50.0)	2 (7.7)	39 (54.2)	20 (29.4)	21 (70.0)	18 (28.6)	23 (65.7)	41 (41.8)
Low FFMI	20 (80.0)	45 (61.6)	24 (72.7)	36 (60.0)	25 (96.2)	40 (55.6)	52 (81.3)	13 (38.2)	50 (79.4)	19 (48.7)	65 (66.3)
Normal FFMI	5 (20.09)	28 (38.4)	9 (27.3)	24 (60)	1 (3.8)	32 (44.4)	12 (18.8)	21 (61.8)	13 (20.6)	20 (51.3)	33 (33.7)
Total	24 (24.5)	73 (75.5)	60 (64.5)	33 (35.5)	26 (26.5)	72 (73.5)	74 (74.7)	25 (25.3)	63 (64.3)	35 (35.7)	98 (100)

high magnitude of malnutrition, occurred in patients with HSCT. The prospective longitudinal cohort study by Barritta de Defranchi et al. showed that 59.7% of patients with HSCT were malnourished. In our study, we found that the malnutrition magnitude differences among the PG-SGA scale, GLIM criteria, and GLIM-China were 75.5, 80.6, and 64.3%, respectively, which was basically consistent with the study by Barritta de Defranchi et al. (14) and Brotelle et al. (15).

The definition of malnutrition is debated recently. No single existing approach has secured broad global acceptance (6, 16–20). The advantage of GLIM is that it can evaluate the nutritional status more simply and accurately by incorporating objective muscle mass data into the evaluation. However, the FFMI and ASMI cutoff values measured by using the BIA method are not based on Chinese population standards. Therefore, some researchers in China define malnutrition by using the GLIM criteria without muscle mass data, as mentioned earlier (2). However, Jingyong Xu showed that nutritional support therapy after the GLIM assessment removed muscle mass and neglected the benefits of reducing infection complications (13). In our previous research, we also found that some IBD patients with muscle mass reduction cannot be identified by commonly used nutrition assessment scales such as NRS-2002 (21). Our team has considered whether GLIM-China has an impact on malnutrition diagnosis. We also found a suitable population to confirm the role of muscle mass in malnutrition diagnosis. According to the NRS-2002 part of "Severity of disease," patients with HSCT at least have a score of 3, indicating that patients with HSCT are all at nutrition risk, and thus can enter into the second step of GLIM; hence, they are suitable for learning the diagnosing malnutrition significance between primary GLIM and GLIM-China criteria.

Appendicular skeletal muscle mass and FFMI were recommended by ESPEN. BIA, which had good consistency with DEXA, was used to measure the ASMI and FFMI of patients with HSCT (22). We found that normal FFMI (FFMI $\geqq$ 17 kg/m^2 for men or >15 kg/m^2 for women) and GLIM-China (-) diagnosed malnutrition were generally consistent with each other, possibly related to the inclusion of FFMI in the process of GLIM-China. Consistency was shown between ASMI and GLIM-China in the assessment of malnutrition but with a poor agreement. The low ASMI rate (58.2%) is lower than the GLIM-China (+) rate (64.3%). So, GLIM-China cannot be replaced by ASMI because many nutrition-related factors are included in it such as weight, food intake, inflammation, and disease.

PG-SGA is a widely used tool to detect patients with malnutrition or at risk of malnutrition (9). We found that PG-SGA and ASMI are parallel in the diagnosis of malnutrition, and there is good agreement between the two methods. Similarly, PG-SGA and FFMI are consistent in the diagnosis

TABLE 5 Logistic analysis between CRP/ESR and GLIM-China/PG-SGA.

	B.	S.E.	Wald	df	*p*	Odds ratio	95%CI for odds ratio	
							Lower	Upper
GLIM-China								
CRP	0.014	0.021	0.457	1	0.499	0.972	0.973	1.057
ESR	0.020	0.011	3.266	1	0.071	1.048	0.998	1.043
PG-SGA								
CRP	0.012	0.028	0.185	1	0.139	1.012	0.959	1.068
ESR	0.039	0.015	6.410	1	0.004	1.040	1.009	1.072

of malnutrition, but there is no difference between the positive rates. In this study, we found that 38.2% of patients had normal nutrition by PG-SGA but with low FFMI, and 30% of whom had low ASMI. Interestingly, 40% of patients had normal nutrition by GLIM-China with low FFMI, and 34% had low ASMI. It is clear that if only the PG-SGA scale is used as a diagnostic criterion for evaluating malnutrition, a large proportion of patients with reduced muscle mass will be missed, but a larger number of patients will be missed by GLIM-China. If the value of ASMI and FFMI is included in the GLIM criteria, patients with low FFMI or low ASMI can be diagnosed with GLIM (+), which may effectively avoid the missed diagnosis of malnutrition. Therefore, compared with GLIM-China and PG-SGA, we propose that both FFMI and ASMI can also be used to diagnose malnutrition. GLIM-China is less sensitive than PG-SGA for diagnosing malnutrition in patients with HSCT (Figures 1, 2). If the standard of FFMI and ASMI is adopted in GLIM, the positive result of GLIM will be the same as the result showed low FFMI and low ASMI. In addition, compared with GLIM, using GLIM-China may lose some patients who need nutritional therapy.

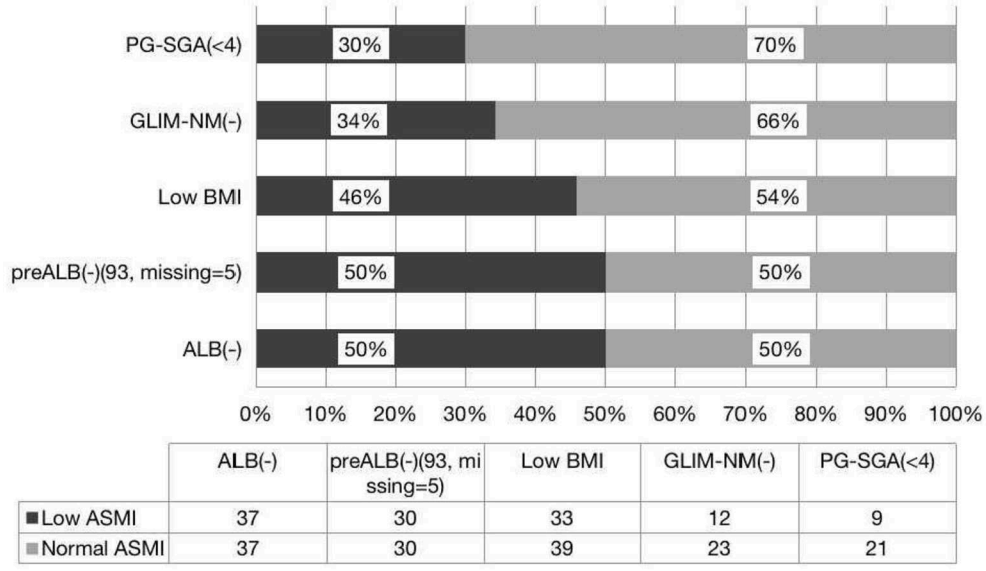
Hypoproteinemia increases bacteremia and mortality in patients with hematopoietic stem cell transplants. The albumin level in serum is affected by many factors such as inflammation, infection, liver damage, and fluid status. Therefore, albumin was no longer recommended for identifying malnutrition by the Academy of Nutrition and Dietetics (AND) and ASPEN (1, 19). We set 35 g/L as the cutoff value for this study because it has commonly been used as evidence of malnutrition in hospitalized elderly patients (23). Our data indicated that hypoproteinemia occurred in 16.3% of patients during peri-hematopoietic stem cell transplantation (24), which was less than the positive rate of PG-SGA, GLIM, and GLIM-China. Compared with albumin, serum pre-albumin is considered a more sensitive indicator of nutritional status, which has also been used as a blood marker for malnutrition. A meta-analysis revealed that pre-albumin concentrations <20 mg/dL may indicate malnutrition (25), so we chose this value as the cutoff value for the current study. Our study found that 35.5% of patients had low pre-albumin levels and 50% of those with normal pre-albumin had low ASMI, 60% of those with normal pre-albumin patients had low FFMI, 50% of those with normal albumin had low ASMI, and 61.6% of those with normal albumin had low FFMI. Thus, these results indicated that ASMI and FFMI cannot be replaced by albumin and pre-albumin.

Inflammation is listed in the GLIM as one of the indicators that may cause malnutrition. It has been suggested that the loss of muscle mass may be related to changes in skeletal muscle mitochondria, leading to ROS generation-mediated inflammation-induced skeletal muscle cell apoptosis (26, 27). CRP reflects the level of acute inflammation (28), and our samples were generally collected when patients' condition was relatively stable, such as before HSCT or 2 weeks after the infusion of stem cells. The ESR is another widely used inflammation indicator. Since the ESR does not change rapidly at the beginning of the inflammation process, and the normalization rate is slower than other acute-phase reactants, we also analyzed the ESR and muscle mass reduction. However, we found that CRP and ESR had no correlation with the decline of FFMI and ASMI. Therefore, muscle mass reduction cannot be replaced by serum inflammation indicators. Similarly, regression analysis results suggested that both CRP and ESR are lacking specificity in the diagnosis of malnutrition.

One limitation of our research is the relatively low number of enrolled patients. Due to the lack of large prospective randomized controlled study data to identify the cutoff value of muscle mass reduction for Chinese patients, we just used the sarcopenia standard of Asia (10), which may have caused some bias. More prospective studies with larger sample sizes are needed to confirm our findings.

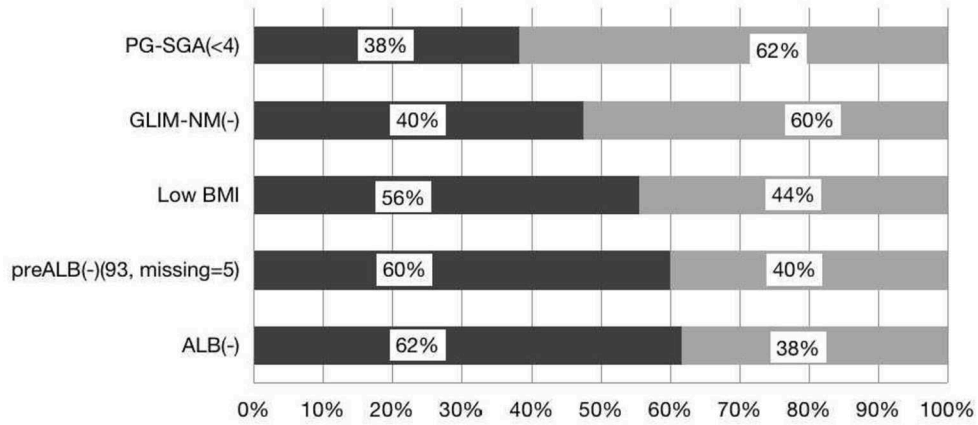
5. Conclusion

A high nutrition risk rate (100%) and malnutrition prevalence rate are common among patients with HSCT; FFMI



	ALB(-)	preALB(-)(93, missing=5)	Low BMI	GLIM-NM(-)	PG-SGA(<4)
Low ASMI	37	30	33	12	9
Normal ASMI	37	30	39	23	21

FIGURE 1
Consistence of the ASMI with the nutritional scales/parameters in the nutritional assessment of patients with HSCT.



	ALB(-)	preALB(-)(93, missing=5)	Low BMI	GLIM-NM(-)	PG-SGA(<4)
Low FFMI(+)	45	36	40	19	13
Normal FFMI	28	24	32	21	21

FIGURE 2
Consistence of the FFMI with the nutritional scales/parameters in the nutritional assessment of patients with HSCT.

and ASMI are helpful for finding malnourished patients with HSCT who are missed by the PG-SGA scale and GLIM-China. If only the PG-SGA scale is used as a diagnostic criterion for evaluating malnutrition, a large proportion of patients with reduced muscle mass will be missed, but more patients with muscle loss will be missed *via* GLIM-China.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by NCT04591340. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

FG and LM designed this study. FG and LC performed the research, analyzed data, and wrote the manuscript. FG, LC, LM, LHo, TC, WM, LHu, WJ, and WW collected the study data. All authors read and approved the final version of this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The role of predicted lean body mass and fat mass in non-alcoholic fatty liver disease in both sexes: Results from a secondary analysis of the NAGALA study

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Objective: High body mass index (BMI) is an important risk factor for non-alcoholic fatty liver disease (NAFLD). However, the association of body composition such as fat mass (FM) and lean body mass (LBM) with NAFLD has not been adequately studied. The purpose of this study was to clarify the contribution of body composition FM and LBM to NAFLD.

Methods: We analyzed data from 7,411 men and 6,840 women in the NAGALA cohort study. LBM and FM were estimated for all subjects using validated anthropometric prediction equations previously developed from the National Health and Nutrition Examination Survey (NHANES). Using multiple logistic regression and restricted cubic spline (RCS) to analyze the association and the dose-response curve of predicted LBM and FM with NAFLD in both sexes.

Results: The prevalence of NAFLD in man and woman subjects was 27.37 and 6.99%, respectively. Predicted FM was positively and linearly associated with NAFLD in both sexes, with each 1 kg increase in predicted FM associated with a 27 and 40% increased risk of NAFLD in men and women, respectively. In contrast, predicted LBM was negatively associated with NAFLD in both sexes, with each 1 kg increase in predicted LBM reducing the risk of NAFLD by 4 and 19% in men and women, respectively. In addition, according to the RCS curve, the risk of NAFLD did not change in men when the predicted LBM was between 47 and 52 kg, and there seemed to be a saturation effect; further, the threshold value of the saturation effect was calculated to be about 52.08 kg by two-piecewise logistic regression, and the protective effect on NAFLD would be significantly enhanced when the man predicted LBM was greater than 52.08 kg.

Conclusion: The current findings suggested that body composition LBM and FM had opposite associations with NAFLD in both sexes, with higher LBM associated with a lower risk of NAFLD and higher FM increasing the risk of NAFLD, especially in women.

KEYWORDS

non-alcoholic fatty liver disease, predicted lean body mass, body mass index, predicted fat mass, LBM

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by excessive intrahepatocellular fat deposition due to etiologies other than alcohol and other well-defined factors of liver damage, and is an important risk factor for the development of end-stage liver disease, liver transplantation, and cardiovascular mortality (1, 2). The main causes of NAFLD are over nutrition and obesity (3), and epidemiological surveys have shown that the prevalence of NAFLD is increasing in parallel with obesity and diabetes (4); it is estimated that more than a quarter of the world's population has NAFLD, and the prevalence is as high as 80% in obese people (5). However, NAFLD is not exclusive to the obese population, and a specific group of NAFLD has attracted increasing attention in recent years, namely non-obese/lean NAFLD (6); they have a normal or even low BMI, but this group of patients also has long-term intra- and extra-hepatic comorbidities and even a higher risk of liver-related events than obese NAFLD (7, 8).

High BMI is a recognized risk factor for NAFLD, however, the main risk factors and pathophysiological mechanisms of lean NAFLD are unknown and may be related to genetic factors and reduced skeletal muscle mass and function (9). Therefore, a key task is to further investigate the independent role of two major components of BMI, FM, and LBM, on the risk of NAFLD on the basis of clarifying the correlation between BMI and NAFLD risk. However, most similar studies have investigated the association of only one body composition with NAFLD risk (10–12), and only one cross-sectional study in a European elderly population investigated the independent effects of both FM and LBM on NAFLD risk (13). Considering the differences in body composition between different ethnic populations and the fact that there is currently no evidence of the correlation between body composition indicators (14) and NAFLD in the general population, the current study aimed to explore the independent association of LBM and FM with NAFLD in the general population in Asia based on the NAGALA study.

Materials and methods

Study design and population

The current study is a cross-sectional analysis of data from subjects in the NAGALA study cohort. The study design and purpose of the NAGALA cohort have been previously described in detail (15). In short, this research project has been continuously recruiting the general population who underwent health checkups at Murakami Memorial Hospital since 1994, and analyzing their examination data for the early detection of chronic diseases and their risk factors that have a significant impact on public health, and providing reference materials for the formulation of chronic disease prevention policies and clinical control. The NAGALA study has received ethical approval from the Murakami Memorial Hospital Ethics Committee and informed consent from the subjects (IRB2018-09-01), and the study dataset has been uploaded to the Dryad database by Prof. Okamura (16); other investigators were authorized to freely use the data from the study for secondary analysis without violating the terms of the database.

We extracted data from the Dryad database for 20,944 subjects recruited in the NAGALA cohort prior to 2016 and further excluded 1,131 subjects diagnosed with diabetes or fasting glucose above 6.1 mmol/L (impaired fasting glucose) at baseline, 416 subjects with liver disease (other than fatty liver), 1,952 subjects with excessive alcohol consumption (17), 2,321 subjects on medication at baseline, 863 subjects with incomplete examination data, and 10 subjects who withdrew from the study for unknown reasons according to the study objectives. The analysis of the data of all subjects in the current study complied with the Declaration of Helsinki, seeing STROBE statement (S1 Text), and was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (IRB2021-066).

Collection and definition of anthropometric, clinical, and biochemical indicators

Information on age, lifestyle habits (smoking status, exercise habits, drinking status), sex, previous illnesses, and medication use were collected by professional medical staff based on a standardized questionnaire submitted by each subject, and standing systolic and diastolic blood pressure (S/DBP), waist circumference (WC), weight, height, and BMI were measured in the room using standard methods. In addition, lifestyle habits were stratified according to the following criteria: exercise habits: exercise at least once a week; smoking status: subjects were classified as none/past/present smokers according to their smoking history; and drinking status: no or small/light/moderate drinking according to weekly alcohol consumption (17).

Blood specimens from subjects in a fasting state (at least 8 h fasting) were analyzed using the automatic biochemical analyzer in the laboratory to obtain concentrations of various biochemical parameters, including fasting glucose (FPG), triglycerides (TG), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-density lipoprotein cholesterol (HDL-C), Glycosylated hemoglobin (HbA1c), and total cholesterol (TC).

Calculation of predicted FM and LBM

The predicted FM and LBM were calculated using anthropometric prediction equations (**Table 1**), which were developed and validated by Lee et al. from data extracted from the NHANES database of 14,065 subjects who had undergone dual-energy X-ray absorptiometry (DXA) examinations (18). Lee et al. incorporated the subject's demographic information and anthropometric indicators into the multiple linear regression model as predictor variables, and continuously adjusted the included predictor variables to fit the linear regression models with the highest agreement with the actual FM and LBM measured by DXA. Ultimately, they found that linear regression models using height, WC, age, weight, and race as predictor variables had the highest consistency [LBM (women: R^2 = 0.85; men: R^2 = 0.91)] and [FM (women: R^2 = 0.93; men: R^2 = 0.90)].

Diagnosis of NAFLD

As previously described (15), abdominal ultrasound was first performed on all subjects by a sonographer, and then a specialist

TABLE 1 Anthropometric prediction equations for lean body mass (LBM) and fat mass (FM) developed from the National Health and Nutrition Examination Survey.

Lean body mass
Men 19.363 + 0.001 * age (year) + 0.064 * height (cm) + 0.756 * weight (kg)–0.366 * waist circumference (cm) –1.007
Women −10.683–0.039 * age (year) + 0.186 * height (cm) + 0.383 * weight (kg)–0.043 * waist circumference (cm)–0.340
Fat mass
Men −18.592−0.009 * age (year)−0.080 * height (cm) + 0.226 * weight (kg) + 0.387 * waist circumference (cm) + 1.050
Women 11.817 + 0.041 * age (year)–0.199 * height (cm) + 0.610 * weight (kg) + 0.044 * waist circumference (cm) + 0.325

gastroenterologist diagnosed NAFLD based on a combination of liver brightness, clarity of liver vessels, liver and kidney echo contrast and depth attenuation without any other information about the subjects (19).

Statistical analysis

All analyzes in the current study were stratified by sex because of the sex-specific differences in body composition and the markedly different disease incidences and health outcomes associated with the sex (20). R language version 3.4.3 and Empower (R) version 2.0 were used for all analysis steps in this study and a two-sided $P < 0.05$ was considered significant.

Descriptive analysis: First, subjects of both sexes were divided into two groups according to whether they had NAFLD or not, and all data except lifestyle habits were described by mean (standard deviation) or median (25th, 75th percentile) according to whether they were normally distributed or not, while for lifestyle habits (smoking status, exercise habits, drinking status) data were described using frequency (%). Subsequently, to compare and quantify the differences between the Non-NAFLD and NAFLD groups, we calculated the weighted standardized difference values between the groups (>10% was considered significant) using the inverse probability of treatment weighting method (21).

Correlation analysis: First, all covariates were screened for collinearity using multiple linear regression analysis (22), and the final covariates with a variance inflation factor (VIF) greater than 5 were defined as collinear variables. Then, constructed four multivariate logistic regression models to examine the associations between predicted FM and LBM and BMI and NAFLD according to the recommendations of the STROBE guidelines (23), and in all models predicted FM and LBM were adjusted for each other and all collinear covariates were excluded. Model 1 was adjusted for age and lifestyle habits (smoking status, exercise habits, drinking status); model 2 considered the effect of liver function indicators (ALT, AST, GGT) on the association based on model 1; model 3 was further adjusted for glycemic parameters (FPG, HbA1c) based on model 2; finally, model 4 considered the effect of lipid parameters (TC, TG, HDL-C) on the association based on model 3.

Non-linear and threshold analyses: To further explore the effect of changes in predicted FM and LBM on NAFLD risk, this study fitted dose-response relationship curves between predicted FM and LBM and NAFLD risk based on model 4 using the RCS regression model with 4-knot. In addition, if a non-linear association was found between the

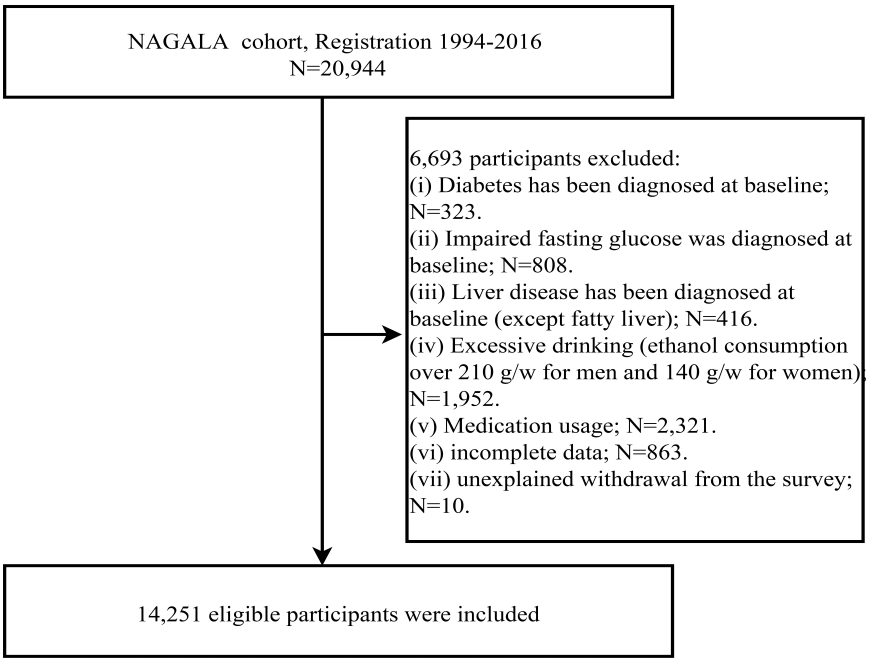

FIGURE 1
Flowchart of the selection process of study subjects.

predicted FM and LBM of both sexes and NAFLD, the two-piecewise logistic regression model was further used to find the optimal inflection point on the curve, i.e., the value of the inflection point corresponding to the model with the maximum likelihood estimate.

Results

Study subjects and characteristics

After a further screening of the original data set, a total of 14,251 subjects were included in the current study (Figure 1), including 7,411 men with a mean age of 43.82 years and 6,840 women with a mean age of 43.22 years; the prevalence of NAFLD was 27.37 and 6.99% in men and women, respectively. Table 2 describes the basic data of subjects of both sexes grouped according to whether they had NAFLD or not. By looking at standardized difference values between the Non-NAFLD and NAFLD groups in both sexes, we found significant differences in most baseline parameters; subjects with NAFLD tended to have higher weight, BMI, predicted LBM, WC, predicted FM, ALT, GGT, AST, TG, TC, FPG, SBP, DBP, HbA1c levels, and lower HDL-C levels and less drinker, with obesity-related indicators predicted FM (standardized difference: 153% for women; 122% for men), WC (standardized difference: 154% for women; 122% for men), and BMI (standardized

TABLE 2 Baseline characteristics of subjects grouped by sex and non-alcoholic fatty liver disease (NAFLD).

Characteristic	Men			Women		
	Non-NAFLD	NAFLD	Standardize diff. % (95% CI)	Non-NAFLD	NAFLD	Standardize diff. % (95% CI)
No. of subjects	5,382	2,029		6,362	478	
Age, year	42.00 (36.00–50.00)	43.00 (38.00–50.00)	5 (0, 10)	42.00 (36.00–49.00)	49.00 (41.00–54.00)	56 (46, 65)
Weight, kg	64.65 (8.34)	74.30 (10.56)	101 (96, 107)	51.86 (7.06)	63.17 (9.97)	131 (121, 141)
Height, m	1.71 (0.06)	1.71 (0.06)	5 (1, 10)	1.58 (0.05)	1.57 (0.05)	25 (16, 34)
BMI, kg/m^2	22.12 (2.42)	25.48 (3.02)	123 (117, 128)	20.67 (2.57)	25.58 (3.57)	158 (148, 168)
WC, cm	77.99 (6.77)	86.62 (7.37)	122 (116, 127)	70.80 (7.30)	83.27 (8.86)	154 (144, 163)
LBM$^{\&}$, kg	49.30 (46.43–52.66)	52.98 (49.59–57.54)	75 (70, 81)	33.40 (31.41–35.47)	36.62 (33.93–39.26)	91 (82, 101)
FM$^{\&}$, kg	13.07 (10.32–15.87)	18.15 (15.43–21.35)	122 (117, 128)	16.64 (14.16–19.52)	24.27 (21.06–28.11)	153 (143, 162)
ALT, U/L	18.00 (14.00–23.00)	29.00 (22.00–41.00)	93 (87, 98)	13.00 (11.00–17.00)	19.00 (15.00–26.00)	63 (54, 73)
AST, U/L	17.00 (14.00–21.00)	21.00 (17.00–26.00)	54 (49, 60)	16.00 (13.00–19.00)	18.00 (15.00–22.00)	35 (26, 44)
GGT, U/L	17.00 (14.00–24.00)	24.00 (18.00–35.00)	44 (38, 49)	12.00 (9.00–14.00)	15.00 (12.00–20.00)	51 (41, 60)
HDL-C, mmol/L	1.30 (1.10–1.54)	1.11 (0.96–1.28)	68 (63, 73)	1.63 (1.40–1.89)	1.33 (1.16–1.56)	79 (70, 89)
TC, mmol/L	5.06 (0.84)	5.41 (0.85)	42 (37, 47)	5.05 (0.86)	5.56 (0.92)	57 (47, 66)
TG, mmol/L	0.80 (0.58–1.16)	1.32 (0.91–1.86)	75 (70, 80)	0.54 (0.40–0.77)	1.02 (0.73–1.38)	96 (87, 106)
FPG, mmol/L	5.25 (0.37)	5.42 (0.35)	48 (43, 53)	4.96 (0.38)	5.27 (0.40)	79 (70, 88)
HbA1c, %	5.13 (0.31)	5.27 (0.33)	45 (40, 50)	5.17 (0.32)	5.42 (0.33)	78 (69, 87)
SBP, mmHg	116.04 (13.16)	124.04 (14.46)	58 (53, 63)	108.42 (13.77)	120.71 (16.04)	82 (73, 92)
DBP, mmHg	72.88 (9.32)	78.44 (10.08)	57 (52, 62)	67.00 (9.48)	75.11 (10.22)	82 (73, 92)
Exercise habits, *n* (%)			13 (8, 18)			5 (0, 14)
No	4,300 (79.90%)	1,720 (84.77%)		5,351 (84.11%)	410 (85.77%)	
Yes	1,082 (20.10%)	309 (15.23%)		1,011 (15.89%)	68 (14.23%)	
Drinking status, *n* (%)			25 (20, 30)			16 (6, 25)
Non/small	3,731 (69.32%)	1,623 (79.99%)		5,986 (94.09%)	465 (97.28%)	
Light	1,096 (20.36%)	273 (13.45%)		376 (5.91%)	13 (2.72%)	
Moderate	555 (10.31%)	133 (6.55%)				
Smoking status, *n* (%)			6 (1, 11)			4 (0, 14)
None	1,952 (36.27%)	758 (37.36%)		5,609 (88.16%)	427 (89.33%)	
Past	1,538 (28.58%)	615 (30.31%)		382 (6.00%)	24 (5.02%)	
Current	1,892 (35.15%)	656 (32.33%)		371 (5.83%)	27 (5.65%)	

Values were expressed as mean (standard deviation) or medians (quartile interval), or *n* (%).
BMI, body mass index; WC, waist circumference; LBM, lean body mass; FM, fat mass; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure.
$^{\&}$Derived from validated anthropometric prediction equations.

TABLE 3 The odds ratio of associations between predicted fat mass (FM) and lean body mass (LBM) and body mass index (BMI), and non-alcoholic fatty liver disease (NAFLD) risk.

	OR (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
Men				
BMI	1.43 (1.40, 1.47)	1.32 (1.29, 1.36)	1.47 (1.43, 1.51)	1.41 (1.37, 1.45)
LBM[&]	0.92 (0.91, 0.94)	0.95 (0.93, 0.97)	0.95 (0.93, 0.97)	0.96 (0.94, 0.98)
FM[&]	1.43 (1.40, 1.47)	1.32 (1.29, 1.36)	1.32 (1.29, 1.35)	1.27 (1.24, 1.31)
Women				
BMI	1.58 (1.52, 1.63)	1.54 (1.48, 1.59)	1.48 (1.43, 1.54)	1.42 (1.37, 1.48)
LBM[&]	0.75 (0.70, 0.80)	0.77 (0.72, 0.82)	0.78 (0.73, 0.84)	0.81 (0.76, 0.87)
FM[&]	1.55 (1.48, 1.62)	1.51 (1.44, 1.58)	1.46 (1.39, 1.53)	1.40 (1.33, 1.47)

Model 1 adjusted for age, exercise habits, drinking status, and smoking status.
Model 2 adjusted for age, exercise habits, drinking status, smoking status, ALT, AST, and GGT.
Model 3 adjusted for age, exercise habits, drinking status, smoking status, ALT, AST, GGT, FPG, and HbA1c.
Model 4 adjusted for age, exercise habits, drinking status, smoking status, ALT, AST, GGT, FPG, HbA1c, TC, TG, and HDL-C.
Both predicted LBMI and predicted FMI were mutually adjusted for each other. Abbreviations as in Table 2.
[&]Derived from validated anthropometric prediction equations.

difference: 158% for women; 123% for men) having the largest standardized difference values. In addition, exercise habits differed significantly only between the man subject groups, age and height differed significantly only between the woman subject groups, and smoking status did not differ significantly between the Non-NAFLD and NAFLD groups in either sex. It is worth mentioning that the prevalence of NAFLD was much higher in men than in women, almost four times.

Association of body composition and BMI with NAFLD

Supplementary Table 1 shows the results of collinearity screening, where WC, height, weight, and DBP were defined as collinear variables and excluded from the multivariate logistic regression models. To exclude the influence of confounding factors on the association as much as possible, we developed four stepwise adjusted multiple logistic regression models based on the epidemiology of NAFLD (Table 3). In model 1 with preliminary adjustment for age and lifestyle habits, predicted FM and BMI for both sexes were associated with increased risk of NAFLD, whereas predicted LBM was resistant to NAFLD risk for both sexes; in model 4, which further adjusted for liver function parameters, glycemic parameters, and lipid parameters, the direction of the associations between predicted FM and LBM and BMI and NAFLD remained the same and the magnitude of the associations changed only slightly, with each 1 kg increment in predicted LBM being associated with a 4% reduction in NAFLD risk in men (OR 0.96, 95% CI 0.94, 0.98) and a 19% reduction in NAFLD risk in women (HR 0.81, 95% CI 0.76, 0.87), whereas each 1 kg increment in predicted FM was associated with a 27% increased risk of NAFLD in men (HR 1.27, 95% CI 1.24, 1.31) and a 40% increased risk of NAFLD in women (HR 1.40, 95% CI 1.33, 1.47). Overall, body composition indicators predicted LBM and FM had opposite associations with NAFLD in both sexes, with higher predicted LBM associated with a lower risk of NAFLD, which was more protective in women than in men; in addition, higher predicted FM increased the risk of NAFLD, especially in women.

Non-linear analysis and threshold effect analysis of predicted FM and LBM with NAFLD

To visualize the association between the continuous variables predicted FM and LBM and the risk of NAFLD, we nested the RCS regression model with 4-knot into model 4 to fit the dose-response curves between predicted FM and LBM and the risk of NAFLD in both sexes. A non-linear association of predicted LBM with NAFLD in men could be seen in Figure 2, where the risk of developing NAFLD did not change when the predicted LBM was between 47–52 kg, showing a saturation effect, while in women the predicted LBM was linearly associated with NAFLD. Moreover, from Figure 3, we observed that the predicted FM was linearly associated with the risk of NAFLD in both sexes. Subsequently, we further calculated the optimal inflection point on the dose-response relationship curve between predicted LBM and NAFLD risk in men using a two-piecewise logistic regression model by the point-taking method and found that when the predicted LBM was less than 52.08 kg, the OR value of each 1 kg increment associated with the risk of NAFLD in men was 0.98, while when the predicted LBM was greater than 52.08 kg, the protective effect on NAFLD was stronger, with an OR value of 0.94 (Table 4).

Discussion

In this large general population-based study, we analyzed the association of BMI and body composition indicators, predicted FM and LBM, with the risk of NAFLD. Consistent with the conventional view, this study found that BMI was associated with an increased risk of NAFLD in both sexes and that there was no significant difference in the effect of BMI on NAFLD in both sexes. However, this study revealed for the first time in the general population that predicted FM and LBM, components of BMI, were oppositely associated with NAFLD risk and had stronger effects on NAFLD in women than in men; where predicted LBM was negatively associated with the risk of NAFLD in both sexes and predicted FM was a common risk factor for

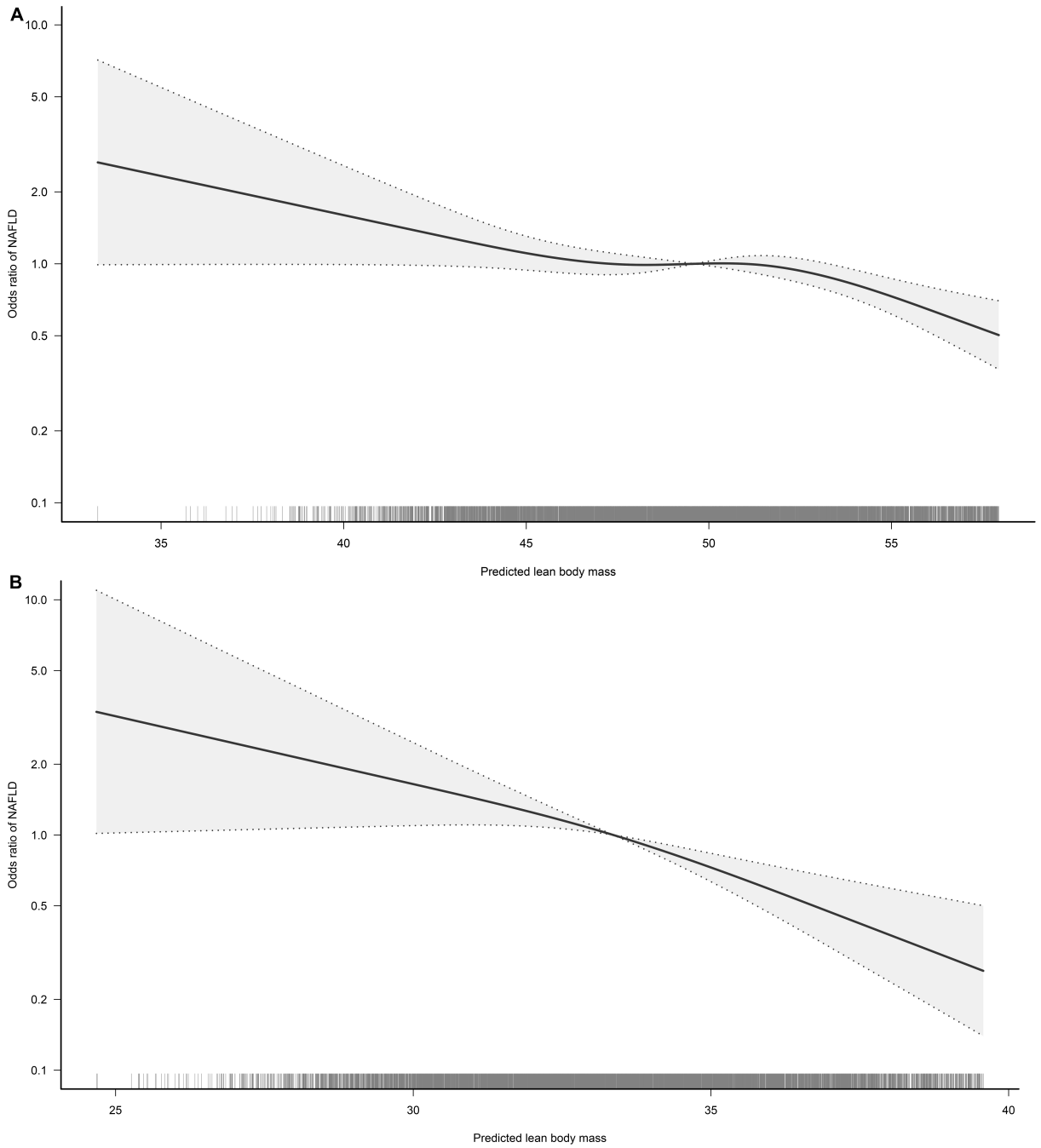

FIGURE 2
Restricted cubic spline analysis of predicted lean body mass (LBM) for the estimation of the risk of non-alcoholic fatty liver disease (NAFLD) in men **(A)** and women **(B)**. Adjusted for age, exercise habits, drinking status, smoking status, ALT, AST, GGT, FPG, HbA1c, TC, TG, HDL-C, and FM.

NAFLD in both sexes. It is worth mentioning that the protective effect of predicted LBM on NAFLD in men was variable and will be further enhanced when the predicted LBM in men was greater than 52.08 kg.

In recent years, with the great increase in economic and material standards worldwide, a lifestyle of high energy intake and low energy consumption has become mainstream, and therefore obesity-related diseases have become the chronic diseases that have the greatest impact on the health of the general population, with almost parallel increases in the prevalence of diabetes, hypertension, metabolic syndrome, and NAFLD (4, 5, 24, 25). Previous studies have shown that insulin resistance (IR) is a core pathophysiological mechanism shared by NAFLD and these obesity-related diseases (3, 26, 27); IR is a pathological state in which the body develops compensatory hyperinsulinemia due to various factors that lead to reduced insulin-promoted glucose uptake and utilization (28). Therefore, further exploration of body parameters with important effects on insulin sensitivity may deepen our understanding of the relationship between obesity and NAFLD risk and provide new insights into the study of risk factors and pathogenic mechanisms of lean NAFLD.

Although a significant association between BMI, an indicator of obesity, and the risk of NAFLD has now been found in a large number of observational studies, BMI as a proxy measure of

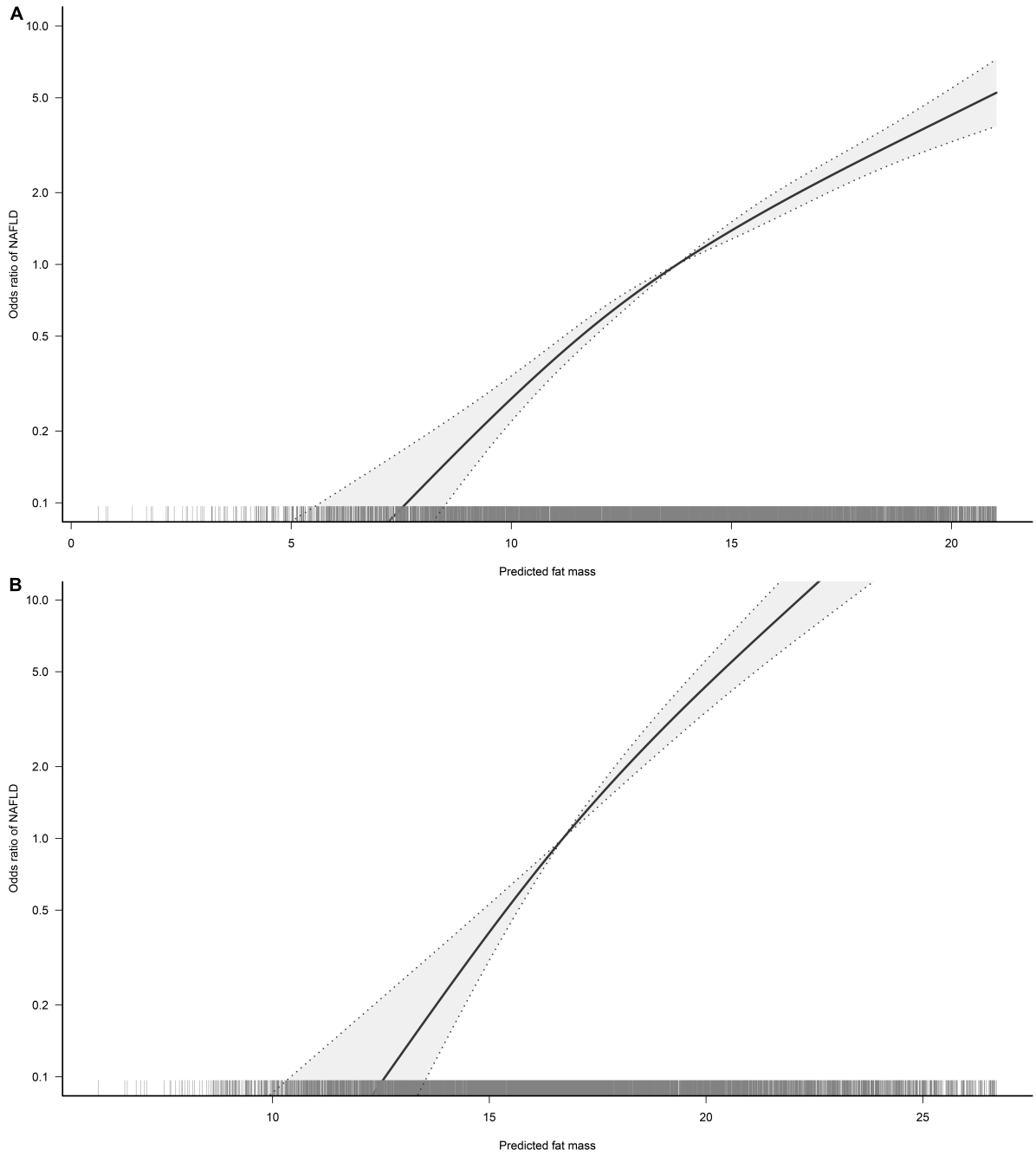

FIGURE 3
Restricted cubic spline analysis of predicted fat mass (FM) for the estimation of the risk of non-alcoholic fatty liver disease (NAFLD) in men **(A)** and women **(B)**. Adjusted for age, exercise habits, drinking status, smoking status, ALT, AST, GGT, FPG, HbA1c, TC, TG, HDL-C, and LBM.

general obesity cannot explain the specific role of obesity on insulin sensitivity (29). Evidence from experimental studies suggested that the components of BMI, LBM, and FM, have different effects on insulin-induced regulation of body glucose (30–32). On the one hand, since LBM is overwhelmingly composed of skeletal muscle which is the main body tissue for insulin-induced glucose uptake, and the myofibers of skeletal muscle will release substances such as interleukins and irisin to maintain insulin sensitivity in skeletal muscle cells, a high LBM is more conducive to maintaining stable insulin-induced glucose metabolism (30, 31). On the other hand, excess FM will secrete excessive amounts of cytotoxic substances such as fatty acids, glycerol, and pro-inflammatory cytokines, which would increase IR in peripheral tissues (32); in addition, excessive ectopic deposition of adipose tissue in the liver and skeletal muscle has also been shown to cause IR in the liver and skeletal muscle (33). There is now a large body of evidence from observational studies showing that the two major components of BMI, FM, and LBM, are significantly and independently associated with the risk of obesity-related diseases such as diabetes, cardiovascular disease, and all-cause and cause-specific mortality (34–36), but the relationship between the two and NAFLD was only mentioned in a cross-sectional survey by Alferink et al. (13); their study found that FM and LBM were not significantly associated with NAFLD in an older male population in Europe, while in a normal weight older female population, LBM was significantly

TABLE 4 Piecewise logistic regression examining thresholds for predicted lean body mass (LBM)-related non-alcoholic fatty liver disease (NAFLD) risk in men.

	NAFLD (OR, 95% CI)
	LBM[&]
Fitting model by multivariate logistic regression	
	0.96 (0.94, 0.98)
Fitting model by two-piecewise logistic regression	
The best inflection point	52.08
<inflection point	0.98 (0.95, 1.01)
>inflection point	0.94 (0.91, 0.97)

OR, odds ratios; CI, confidence interval; other abbreviations as in Table 2.
[&]Derived from validated anthropometric prediction equations.

resistant to NAFLD risk (HR 0.84, 95% CI 0.75, 0.94), while FM was significantly associated with an increased risk of NAFLD (HR 1.16, 95% CI 1.03, 1.29). Considering the influence of ethnicity on body composition and that there is no evidence of the correlation between body composition indicators and NAFLD risk in the general population (14), the current study explored for the first time the association of body composition indicators predicted FM and LBM with NAFLD risk in a general population cohort from Asia.

The predicted FM and LBM in this study were calculated using anthropometric prediction equations, which have high predictive performance and have been used to calculate the LBM and FM of subjects in several large studies (18, 34, 36). The current study found significant sex differences in the effects of predicted FM and LBM on NAFLD in the general population, with each 1 kg increase in predicted FM increasing the risk of NAFLD by 40% in women and 27% in men, while each 1 kg increase in predicted LBM decreased the NAFLD risk by 19% in women and 4% in men. Sex differences in this correlation may be related to gender dimorphism in the effects of aging on NAFLD risk and different patterns of fat deposition due to differences in hormone levels in both sexes (37–39); From **Table 2** we found that the age factor was balanced between the Non-NAFLD and NAFLD groups for men, while there was a significant difference between the two groups for women; the mean age of women in the Non-NAFLD group was 42 years, while the mean age of women in the NAFLD group was 49 years, which means that the shift in woman reproductive status that occurs with aging may have an additional impact on the risk of NAFLD. It is well known that women undergo dramatic changes in hormone levels before and after menopause, and that post-menopausal reduction in estrogen levels leads to lower levels of circulating IGF-1, DHEA, GH, and vitamin D as well as increased oxidative stress, and that all of these changes reduce skeletal muscle mass and function through the appropriate mechanisms (37, 40). Furthermore, high levels of estrogen in women can cause excess fat to be stored more in the subcutaneous tissues of the hips and thighs, a relatively healthy fat distribution, whereas men and post-menopausal women have lower levels of estrogen and excess fat tends to be deposited more in skeletal muscle tissue and abdominal visceral organs, dangerous fat distributions that pre-dispose to IR (38–41). Thus, in both men and post-menopausal women populations, except predicted FM, unhealthy fat distribution patterns also mediate a significant portion of BMI-related NAFLD risk.

It is worth mentioning that in the non-linear correlation analysis of this study we found a variable correlation between predicted LBM and NAFLD in men. When predicted LBM was less than 52.08 kg, each 1 kg increment in predicted LBM reduced the risk of NAFLD by 2% in men; after the predicted LBM increased to 52.08 kg, each 1 kg increment in predicted LBM was significantly and independently associated with a 6% reduction in the risk of NAFLD in men. In summary, given the relatively weak effect of body composition on the risk of NAFLD in the men population and the fact that general obesity indicator BMI remains a more important risk factor for NAFLD, we suggested that men should keep their LBM above 52.08 kg on the basis of diet control and weight loss to reduce the risk of NAFLD as much as possible. While the effects of LBM and FM on the risk of NAFLD were relatively greater in women, so performing appropriate resistance training to increase skeletal muscle mass while controlling the diet to reduce fat intake can effectively reduce the risk of NAFLD in women, and precise preventive interventions targeting the single body component may be a new strategy for NAFLD prevention in women.

Study strengths and limitations

The greatest strength of this study is that it is the first to analyze the effect of body composition on the risk of NAFLD in a large sample of the general population, which will provide new insights into preventive interventions for NAFLD. In addition, this study also estimated the potential intervention threshold point of LBM for NAFLD prevention in men by non-linear correlation analysis and threshold effect analysis.

Of course, this study has some limitations: First, body composition indicators, predicted FM and LBM, were calculated by anthropometric prediction equations rather than the gold standard method DXA measurements; furthermore, although Lee et al.'s anthropometric prediction equations take into account the effect of race and have been used to calculate body composition in several published studies in Asian populations (42–44), the high predictive power of the prediction equations has not been directly confirmed in Asian populations at this time and needs to be validated in future studies. Second, the diagnosis of NAFLD was based on abdominal ultrasound images rather than the liver biopsy (19), however, it is unethical to perform an invasive test on the general population attending a health check-up. Third, since this study was a secondary analysis of previous research datasets, some risk factors for NAFLD, such as women's reproductive status, cannot be further obtained, which may cause residual confounding; in addition, since the initial study did not perform bioelectrical impedance analysis on subjects to directly measure FM, this study could not compare the risk assessment ability for NAFLD of the fat mass index, an anthropometric measure with strong risk assessment power for NAFLD, with that of the predicted FM and LBM (45). Fourth, due to the cross-sectional study design, the causal association between body composition and NAFLD risk cannot be analyzed and needs to be verified in future large longitudinal cohort studies.

Conclusion

In conclusion, the results of the current study suggested that increasing LBM can effectively reduce the risk of NAFLD in both sexes, especially in women, while men should keep their LBM above 52.08 kg to minimize the risk of NAFLD; moreover, excessive FM significantly increased the risk of NAFLD. Therefore, adding

appropriate resistance training to increase skeletal muscle mass along with dietary control to reduce fat intake and weight loss is important to prevent NAFLD in both sexes.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Jiangxi Provincial People's Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YZ, SZ, MK, RY, and QX conceived the research, drafted the manuscript, and performed the statistical analysis. YZ revised the manuscript and designed the study. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1103665/full#supplementary-material

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Importance of nutritional assessment tools in the critically ill patient: A systematic review

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Background: Among the risks of the critically ill patient, one of the aspects to be taken into account is the high probability of occurrence of malnutrition risk (40–50%). This process leads to increased morbimortality and worsening. The use of assessment tools allows the individualization of care.

Objective: To analyze the different nutritional assessment tools used during the admission of critically ill patients.

Methods: Systematic review of the scientific literature related to the nutritional assessment of critically ill patients. Between January 2017 and February 2022, articles were rescued from the electronic databases "Pubmed," "Scopus," "CINAHL" and "The Cochrane Library"; which will analyze which instruments are used during nutritional assessment in the ICU, as well as their impact on mortality and comorbidity of patients.

Results: The systematic review was made up of 14 scientific articles that met the selection criteria, obtained from seven different countries. The instruments described were: mNUTRIC, NRS 2002, NUTRIC, SGA, MUST and the ASPEN and ASPEN criteria. All the included studies demonstrated beneficial effects after nutritional risk assessment. mNUTRIC was the most widely used assessment instrument, with the best predictive validity for mortality and adverse outcomes.

Conclusion: The use of nutritional assessment tools makes it possible to know the real situation of patients, and by objectifying situations, to allow different interventions to improve the nutritional level of patients. The best effectiveness has been achieved using tools such as mNUTRIC, NRS 2002 and SGA.

KEYWORDS

nutritional assessment, nutritional support, nutritional therapy, nutritional risk and screening, care management, SGA, NRS 2002, MNA

1. Introduction

In intensive care units (ICU), critically ill patients are at high risk of developing malnutrition, which is associated with worse clinical outcome (1). The nutritional status of critically ill patients deteriorates quite rapidly after admission, as a consequence of severe catabolism caused by stress, proinflammatory cytokines, and hormones, even when patients are well nourished. Ten days after admission, patients may lose 10–25% of their body protein content (exacerbated in those with multiorgan dysfunction syndrome), with losses of up to 10 kg of body weight, depending on the length of stay (2, 3). Critical illness is usually associated with a state of catabolic stress, accompanied by a systemic inflammatory response together with complications related to increased infectious morbidity, multiorgan failure and prolonged hospitalization (4). The scientific literature reports that malnutrition occurs in 40–50% of critically ill patients (with a risk of malnutrition in 35–50% of all patients) (5, 6). The negative effects of malnutrition derive from the correlation between a negative energy balance and an increase in ICU stay (between 5.4 and 6.6 more days of hospitalization), additional days of mechanical ventilation, more frequent infections and higher mortality (data have been found on the threefold relative risk of death among patients with malnutrition, at 1 and 2 years after discharge) (4–9). In addition, a progressive increase in hospitalization costs derived from patient care is suggested, from an average of £5,000 for patients at low risk of malnutrition to an average of over £8,000 for patients at high risk of malnutrition (9–11).

The clinical course of critical illness can be improved by early enteral nutrition (EN), adequate administration of macro- and micronutrients, and strict control of blood glucose. Reductions of up to 35% in the risk of mortality within 30 days of hospital admission have been observed in those patients randomized to early, individualized nutritional therapy (12). Reductions in mortality after nutritional therapy at 90 days (up to 51% of patients), and decreases in the relative risk of overall mortality up to 6 months after discharge (in approximately 27% of hospitalized patients) are also suggested. Reduced readmission rates have been found in patients who received early nutritional support (4, 12, 13).

However, in clinical practice, despite the recommendations of scientific organizations such as the American Society for Parenteral and Enteral Nutrition (ASPEN), nutritional assessment on admission is not a standardized parameter (1). Moreover, tools such as the "Mini Nutritional Assessment" (MNA) are often used, which have not been designed for use in this type of patient, and may therefore lead to underestimation of risk (1, 2). Some useful tools that we can use to perform a nutritional assessment of patients on admission to the ICU are the Subjective Global Assessment (SGA), on the one hand; and, on the other hand, nutritional screening instruments such as the "Nutrition Risk Screening 2002" (NRS 2002), the "Malnutrition Universal Screening Tool" (MUST), the "Nutrition risk in the Critically ill" score (NUTRIC score) or mNUTRIC (modified NUTRIC) (14). Likewise, ASPEN (4) recommends the determination of nutritional risk in all patients admitted to the ICU (1, 2), since from the nutritional assessment it is possible to determine the nutritional diagnosis and establish a correct nutritional intervention (4, 9).

The use of nutritional therapy is aimed at achieving metabolic optimization and attenuation of stress-induced immune responses (derived from critical illness), and not only at avoiding malnutrition (2, 4, 7, 12). Given that, due to their situation, critically ill patients cannot maintain an adequate intake, nutritional therapy is part of the treatment, with early EN being indicated in patients with a functional gastrointestinal tract and hemodynamic stability (4, 7, 13). Thus, in recent years, there has been a transition from the concept of nutritional support to that of nutritional therapy, as the benefits of early administration of EN (before 24–72 h) have been demonstrated in the metabolic response to stress, prevention of oxidative cellular injury and improved immune response (4, 7, 12, 13, 15).

In order to establish adequate and individualized guidelines, it is necessary to carry out an individualized nutritional evaluation in the first hours after admission to hospital units, and mainly in critical care units (4, 9, 14), allowing the detection of the risk of malnutrition, and the early initiation of an adequate nutritional therapy for each person that allows minimizing the adverse effects (9, 13).

This nutritional assessment will include information regarding dietary history; nutrient intake; anthropometric and biochemical measurements; physical, clinical and disease conditions; and functional status (4, 9, 13), and allows the adequacy of supportive therapy to organic functions (4, 13, 15). Thus, the research question that emerges from this systematic review is: What are the benefits of using nutritional status assessment on admission in critically ill patients, and which tools is most effective?

The objective of our study is to identify and describe the tools most commonly used in nutritional assessment in critical care units, and to determine how nutritional assessment and therapy are able to reduce malnutrition and morbidity and mortality in critically ill patients (**Table 1**).

2. Methodology

2.1. Study design

Systematic review of the scientific literature conducted in the year 2022, using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 statement (16). The review protocol was registered in the Prospective International Registry of Systematic Reviews (PROSPERO), with registration number CRD4202222328783.

2.2. Search strategy

The data retrieved for the review was from the last 5 years (01/01/2017 and 01/02/2022). A search was performed in the following electronic databases: "Pubmed," "Scopus," "CINAHL" and "The Cochrane Library." The free and "Mesh" terms used were: "nutrition assessment," "nutritional support," "nutrition therapy," "nutritional risk and screening," "care management," "critical care," "adult." The search was limited to articles found in English, Spanish or Portuguese. The bibliographic references of the retrieved articles were examined with the aim of finding other relevant articles (reverse search). The selected articles were grouped according to the type of study and study variables (most commonly used tools; presence of malnutrition, inflammation or morbimortality analysis in critically ill patients) in order to be able to establish and evaluate the evidence. The bibliographic

TABLE 1 PICO format question.

Research question PICO format	
Patient	Patients admitted to the ICU
Intervention	Nutritional screening and assessment
Comparation	Comparison of nutritional assessment scales
Outcomes	The effect of nutritional assessment on patients' health status

manager "Mendeley Reference Manager" was used to manage the retrieved documents.

The following table (**Table 2**) shows the search strategy used to retrieve the eligible documents in this systematic review, as well as the terms used in each database, the search period selected and the articles obtained.

2.3. Selection criteria

Inclusion criteria: Studies addressing the importance of nutritional screening and assessment on admission of critically ill patients in intensive care units. Evaluation of the predictive capacity of adverse outcomes (malnutrition or inflammation) and mortality. Patients evaluated who are older than 18 years of age. Types of studies: systematic reviews, randomized controlled trials, observational studies and cross-sectional studies (16, 17).

Exclusion criteria: studies on pediatric patients or those belonging to other hospitalization units. Studies focused on pharmaceutical properties of EN or PN or those in which the performance of nutritional risk and complete nutritional assessment is not evaluated. The following types of publication: editorials, letters, legal cases, interviews, book chapters, commentary articles, news, review studies, methodological considerations. Research that is not conducted for humans. Duplicate studies.

2.4. Effect measures

The evaluation of methodological quality was carried out in two phases: first, the evaluation/critical reading of each document and, subsequently, verification of the level of bias. For the quality assessment, the scale adjusted to the corresponding design was used: PRISMA (16), STROBE ("Strengthening the reporting of observational studies in epidemiology") (18) or CASPe ("Critical Appraisal Skills Programme") critical reading (19). As for the assessment of risk of bias, the NOS ("Newcastle-Ottawa") scale was used for longitudinal non-randomized studies (20, 21), the ROB ("Risk-of-bias tool") scale for randomized clinical trials (22) and the ROBIS ("Risk of Bias in Systematic Reviews") scale for systematic reviews (23, 24). The latter two are two instruments recommended by the Cochrane Collaboration (22, 24). For the studies evaluated using the NOS scale, those with scores of less than seven points were defined as having a high level of bias (25, 26).

Finally, the Scottish Intercollegiate Guidelines Network (SIGN) tool (27) was used to evaluate and classify the studies according to the level of evidence.

2.5. Data extraction (selection and codification)

The selection of documents was done first by title and secondly by reading the abstract. The selection was made by two independent investigators to identify studies that potentially met the inclusion criteria described above. For potentially eligible studies, the full text was retrieved and also evaluated by both reviewers for eligibility. A third investigator served as a reviewer in the case of discrepancy between the two. For each study, data were recorded on a form, including the study characteristics (population, study design) and the primary topic (nutritional assessment methods, whether screening or full assessment tools).

TABLE 2 The search strategy.

Database	Search strings	Articles retrieved	Articles selected
Pubmed	(Nutritional assessment) AND (intensive care unit) AND (critical illness) NOT (pediatrics)	71	7
	(((Nutritional risk screening and assessment) AND (intensive care unit) AND (critical illness)) NOT (pediatrics))	60	
	(((Nutrition assessment) AND (intensive care units)) AND (care management)) AND (critical illness)	84	
	((((nutritional assessment) AND (nutritional support)) AND (intensive care units)) AND (critical illness)) AND (tool)	23	
	(((Nutritional assessment) AND (nutritional support)) AND (intensive care units)) AND (nurse)	12	
	((Nutrition assessment) AND (intensive care units)) AND (critical illness)	226	
	((((((Nutrition assessment) AND (intensive care units)) AND (care management)) AND (critical illness)))) AND (nursing care)	13	
Scopus	(Nutritional assessment) AND (intensive care unit) AND (critical illness) NOT (pediatrics)	63	0
Cinahl	(Nutritional assessment) AND (nutritional support) AND (intensive care unit) NOT (pediatrics)	32	3
	(Nutritional assessment) AND (intensive care unit) NOT (pediatrics)	32	
	(Nutritional risk screening and assessment tools) AND (intensive care unit)	11	
Cochrane Library	(Nutritional assessment) AND (nutritional risk and screening) AND (intensive care units) NOT (pediatrics)	15	2
	(Nutritional risk and screening) AND (intensive care units) NOT (pediatrics)	17	

2.6. Data summarization strategy

A narrative synthesis of the findings of the included studies was made, structured according to the type of intervention, the content of the same, the results and the characteristics of the target population.

3. Results

The first search showed a total of 659 articles, of which 12 were finally selected, in addition to 2 articles found by means of a reverse search, so that 14 articles were finally obtained for the systematic review. The selection process is shown in **Figure 1**.

As for the design of the studies, a systematic review (26), a randomized controlled trial (28), 6 retrospective longitudinal studies (3, 29–33), 5 prospective longitudinal studies (34–38) and 1 cross-sectional study (39) were collected. And by provenance, 4 were from China (28, 31, 35, 36), 4 from Brazil (3, 26, 37, 38), 2 from Iran (32, 39), 1 from Israel (29), 1 from the United States (30), 1 from Australia (34) and 1 from Greece (33).

3.1. Evaluation of the level of bias

All the studies included in the present systematic review were rated with a low level of bias (3, 26, 28–33, 35–39) except the one by Egan et al. (34), with a score of 6 on the NOS scale. The longitudinal studies presented a mean of 7.58 points on the NOS scale (21). For the systematic review of Cattani et al. (26) the "Robis" tool (23, 24) was used, with a "low risk of bias" result. In the randomized clinical trial of Liu et al. (28) the "RoB" scale (22) was used, with the same result: "low risk of bias."

3.2. Instruments and criteria used

The most commonly used nutritional assessment tool was mNUTRIC (3, 26, 30–33, 35–39), followed by NRS 2002 (3, 26, 28, 29, 36, 37), NUTRIC (26, 29, 32), SGA (29, 38), MUST (26, 34) and the ASPEN and ESPEN criteria (29) (**Figure 2**).

The mNUTRIC score was scored in all the articles found (3, 26, 29–39) using 5 variables: age, APACHE II score, SOFA score, number of comorbidities, and days since ICU admission. Most authors (3, 30, 31, 33, 35–37, 39) determined that this tool was easier to complete than the original NUTRIC tool, due to the absence of the variable IL-6 (Interleukin-6), which was more difficult to obtain and not all ICUs analyzed had access to this laboratory parameter.

NRS 2002 was the second most used tool (3, 26, 28, 29, 36, 37), where uniformity in its application was also found. First, an initial screening was carried out, taking into account BMI, weight loss, reduction of intake in the last week and severity of the disease. Subsequently, nutritional status and disease severity were assessed more specifically. However, the determination of nutritional risk varied between studies, where some established patients at nutritional risk with a score ≥3 (28, 30, 36), and others with a score ≥5 (3, 29).

NUTRIC was the third most employed tool (26, 29, 32). Age, APACHE II score, SOFA score, number of comorbidities, days since admission to the ICU and the IL-6 parameter. This assessment tool was less employed than its modified version due to IL-6, as it was a difficult value to obtain.

The fourth nutritional assessment tool was the SGA (29, 38). The SGA consisted of a questionnaire that included nutritional history (weight loss, dietary changes, gastrointestinal symptoms), physical examinations performed 24 h post-admission (degree of muscle loss, subcutaneous fat loss or presence of edema) and the impact of the disease.

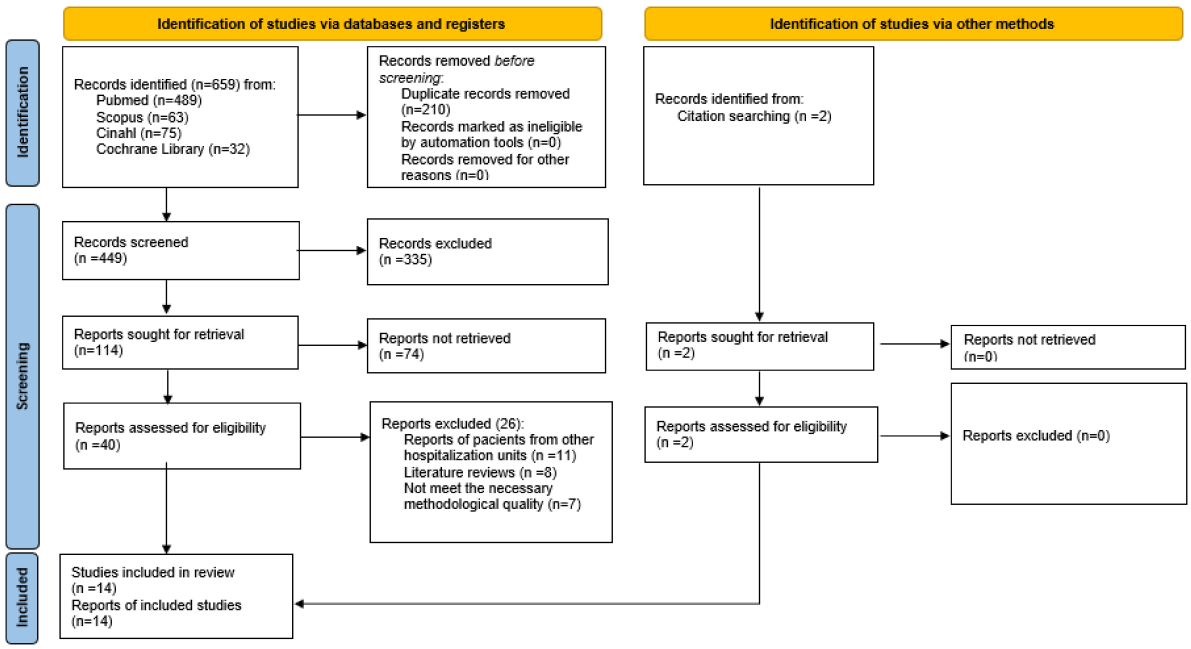

FIGURE 1
Selection process flow chart (PRISMA 2020).

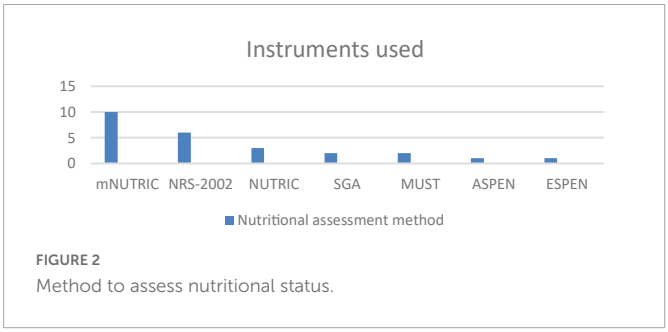

FIGURE 2
Method to assess nutritional status.

MUST was also described by two articles (26, 34). MUST is a 5-step tool that incorporates BMI, weight loss and the effect of acute illness. In this case, the synthesis of the studies offered by Cattani et al. (26) and the prospective study by Egan et al. (34) did find similarities in terms of application and determination of nutritional risk.

Finally, the ASPEN and ESPEN criteria were only described in one article (29), which take into account etiological and phenotypic characteristics of the patients. These criteria are the ones taken into account to determine the diagnosis of malnutrition by these nutrition societies.

The characteristics of the tools were summarized in **Table 3**, showing which parameters are common to the nutritional assessment instruments described above.

3.3. Effects of nutritional assessment

All the included studies (3, 26, 28–39) demonstrated beneficial effects after nutritional risk assessment in critical patients: improving patient prognosis when receiving individualized nutritional therapy (28, 31, 38), identifying patients at nutritional risk with a higher probability of morbidity and mortality who could benefit from nutritional support (26, 29, 32, 33, 35–38) or improving the adequacy of the energy needs of patients admitted to the ICU (30, 39). Correct nutritional screening and assessment allowed the identification of patients who could best benefit from individualized nutritional therapy, as could be seen in the RCT of Liu et al. (28), where patients who received individualized nutritional therapy had a higher rate of improvement in the experimental group (65.1 vs. 45.1%) and the mortality rate was lower than that of the control group (2.3 vs. 6.1%).

These data also correlated with the other results found (26, 31, 35–38), revealing that there was a higher mortality in the groups classified as high nutritional risk by mNUTRIC, NRS 2002 or SGA; so that early nutritional therapy had to be established in these patients to protect them from the risk of malnutrition. The variables most commonly used to determine the benefit of using nutritional assessment tools were mortality (26, 28, 29, 31, 33, 35–38), the presence of comorbidity or complications (3, 26, 28, 31, 32), increased hospital stay or readmissions (31, 35, 37) and the adequacy of energy requirements (26, 30, 39). The analyses for the calculation of

TABLE 3 Components of the different screening tools.

Features	mNUTRIC	NRS 2002	NUTRIC	SGA	MUST	ASPEN	ESPEN
Age	X	X	X				
Apache II	X		X				
SOFA	X		X				
Comorbidities	X		X				
Days of hospital admission	X		X				
IL-6			X				
IMC		X		X	X	X	X
Percentage of weight loss		X			X	X	X
Energy intake compared to energy needs		X				X	X
Severity of illness		X		X	X	X	X
Ener				X	X		
Muscle loss						X	X
Metabolic stress				X			
Physical examination				X			
Nutritional risk classification	<to 3: low risk ≥to 4: high risk ≥5: high risk	<to 3: low risk ≥3: risk ≥to 5: high risk	≤to 5: low risk ≥to 6: high risk	A: well nourished B: moderately malnourished C: severely malnourished	0: low risk 1: medium risk ≥to 2: high risk	Phenotypic criteria: unintentional weight loss, low BMI or loss of muscle mass Etiological criteria: decreased intake or presence of morbidity At least one etiologic criterion and one phenotypic criterion	
Number of studies that have described this tool	11	6	3	2	2	1	1

mortality risk differed according to the types of studies and the tools used:

- Risk of 28-day mortality for patients at high nutritional risk: 87% mortality in the case of Zhang et al. (34) and 67.4% mortality in the study by Wang et al. (35), using mNUTRIC.

- Significant increase in the 28-day mortality rate among patients classified as high nutritional risk using mNUTRIC and NRS 2002 (36). Machado et al. (37) found that patients at high nutritional risk according to mNUTRIC had a threefold increased risk of in-hospital mortality, whereas patients considered at high nutritional risk according to NRS 2002 did not have a statistically higher increased risk of death. The use of the mNUTRIC tool by Gonzalez et al. (38) concluded similar results, detecting a 2.37 and 2.97 times higher mortality risk (depending on the cut-off point used) in patients classified as nutritional risk (score $\geq$ a 5 or $\geq$ a 6); whereas patients classified at risk according to score of $\geq$4 had an almost 6 times higher mortality risk after 28 days than individuals classified without nutritional risk.

- Use of two tools for nutritional assessment: Machado et al. (37) and González et al. (38) proposed the use of mNUTRIC combined with another nutritional assessment tool: NRS 2002 in the first case (37) and SGA in the second (38). Gonzalez et al. (38) suggested that one death could be avoided for every 1.62 patients identified as being at nutritional risk by mNUTRIC and with severe malnutrition (SGA "C") who received an individualized nutritional intervention.

The data shared reveal that the use of any nutritional assessment tool on admission of critically ill patients is effective in detecting the risk of mortality. In addition, other results described were the relationship between nutritional risk and increased risk of presenting comorbidities or longer stay in the ICU (28, 31, 32, 36).

Another way of detecting the positive effects of the use of nutritional assessment instruments could be observed in other studies (30, 39), since the mNUTRIC instrument was proposed to predict energy, protein, carbohydrate and fat intake; because mNUTRIC scores were strongly associated with calorie and protein requirements.

A summary of all the selected papers can be found in the Summary Table (**Table 4**).

4. Discussion

In the present systematic review we found 14 scientific articles (3, 26, 28–39) describing the benefits of using a nutritional assessment tool (mNUTRIC, NRS 2002, NUTRIC, SGA, MUST and ASPEN and ESPEN criteria): prediction of mortality risk for earlier initiation of nutritional therapy (3, 26, 28, 31, 33–38), reduction in the number of complications and length of stay related to malnutrition (3, 26, 28, 32, 36, 38) or improved adequacy of energy requirements (30, 39).

The strengths of this systematic review have been the inclusion of an exhaustive bibliographic search in 4 large electronic databases: "Pubmed," "Scopus," "The Cochrane Library" and "CINAHL" (3 general databases and a specific nursing database), together with the evaluation of the risk of bias of the studies, which has allowed the selection of those with the lowest risk of systematic error. The results found are in agreement with the available scientific evidence (4, 8, 13, 14, 26, 40) showing how critically ill patients can benefit from the use of nutritional assessment tools to improve health and mitigate adverse outcomes. Thus, we can classify these tools as: nutritional risk screening tools (mNUTRIC, NRS 2002, NUTRIC, and MUST) and comprehensive nutritional assessment tools (SGA and the ASPEN and ESPEN criteria).

Most of the longitudinal studies determined the predictive validity of the nutritional screening instruments used (30–32, 35–39), the most analyzed tool with the best predictive capacity for mortality and adverse outcomes being mNUTRIC (3, 26, 30–33, 35–37, 39), as we observed in other scientific studies (41, 42), which suggest that mNUTRIC is a good predictor of mortality in critically ill patients, and that these patients can improve their health status if they are evaluated and given nutritional therapy. However, we detected some unfavorable results after the use of this instrument (29, 34), such as that this tool took longer to complete than others, such as MUST (34). After analysis of these studies, we concluded that they were not too reliable, as they didn't find any tool that was associated with mortality after adjustment for variables or had a high level of bias (29, 34).

Another critique found for the mNUTRIC score was that no nutritional parameters were explicitly taken into account (26). However, the scientific literature (4, 30–33, 35–39, 41–50) gives value to this tool for the following reasons: It has been validated in the critical patient population based on the malnutrition criteria offered by ASPEN (40); it does not contain classical nutritional variables (weight evolution or recent food intake) due to the difficulty of extracting them in ICU patients; the variables used correlate correctly with the pathophysiology of malnutrition, since the degree of inflammation is a determinant factor of nutritional risk, therefore using APACHE II and the SOFA scale is more convenient; the variables related to the number of comorbidities (they consider chronic inflammation) and days of hospitalization in the ICU (they determine reduced intake) are more objective; it has demonstrated predictive validity for mortality, adverse clinical outcomes and increased length of stay of patients; and finally, it is an easy to apply and low cost tool (after elimination of the IL-6 parameter).

Regarding the mNUTRIC cut-off points, most of the scientific literature classifies nutritional risk as a score greater than or equal to 5 (3, 26, 30, 31, 41–44). However, Gonzalez et al. (38) and Wang et al. (35) found that patients classified as nutritional risk with a score greater than or equal to 4 had a higher risk of mortality than those with a score greater than or equal to 5. If nutritional risk could not be determined by mNUTRIC, our results suggest that another tool used to assess the prognosis of critically ill patients is NRS 2002 (3, 26, 28, 37).

Regarding nutritional assessment tools, which according to ASPEN and ESPEN (4, 13, 14) should be performed in all patients at high risk of malnutrition, the only instrument selected in this review was the SGA (29, 38). In the prospective study by Gonzalez et al. (38) we can see how up to 1 death could be avoided for every 1.62 patients identified as being at nutritional risk according to mNUTRIC and classified as SGA "C" (severe malnutrition). These data are in line with the available evidence (8, 13, 42), which shows how SGA has greater predictive validity than other tools (especially for hospital mortality, length of stay, and complications), such as MNA.

TABLE 4 Summary table.

References	Design sample	Intervention tool used	Variables results	Results	Conclusions	Evaluation of the study report/Risk of bias	Level of evidence: SIGN
Egan et al. (34). Australia.	Prospective observational study –20 patients admitted to the ICU on non-invasive mechanical ventilation.	–To compare the time required of patients in whom nutritional screening was completed, using both MUST and mNUTRIC tools in critically ill patients. / -MUST and mNUTRIC.	-Time taken (minutes) to complete nutritional risk screening using both tools. -Barriers found in the use of the nutritional screening tools	-Screening using the MUST tool took less time to complete than screening with mNUTRIC. -The maximum time spent with MUST was 14 minutes, compared with 33 minutes for mNUTRIC.	-MUST is the most feasible nutritional risk screening tool for use in a cohort of ICU patients on non-invasive mechanical ventilation, as it required less time and fewer barriers to completion, as opposed to mNUTRIC.	STROBE: 20/22 / NOS: 6/9	2–
Zhang et al. (36). China.	Prospective observational study. –140 patients admitted to the neurological ICU.	-Investigate the NRS 2002 and mNUTRIC nutritional screening tools in the setting of critically ill neurological patients to predict the prognosis of these patients. / -NRS 2002 and mNUTRIC	-Prevalence of nutritional risk -Mortality of patients at 28 days.	-High nutritional risk as determined by NRS 2002 and mNUTRIC was associated with a significantly increased 28-day mortality rate. -Compared between groups of patients in whom mNUTRIC had been used, those at high nutritional risk according to this tool showed a significantly higher incidence of pulmonary infection, hospital infection, organ dysfunction, and increased 28-day mortality rate, as opposed to those diagnosed at low nutritional risk.	-The mNUTRIC score is independently related to the risk of 28-day mortality in critically ill neurological patients.	STROBE: 22/22 / NOS: 8/9	2 ++
Javid et al. (39). Irán.	Cross-sectional observational study. –1321 patients admitted around 50 ICU's of 25 hospitals in Iran.	-To assess the nutritional adequacy of patients considering the diagnosis and prevalence of malnutrition on admission. / -mNUTRIC	–Nutritional intake. -Classification of patients according to mNUTRIC.	–The mean calorie and protein adequacy was 16.2% and 10.7%, respectively. 16.2% and 10.7%, respectively. -Patients classified as high nutritional risk had a higher adequacy index than those at low nutritional risk.	-The nutritional intake of patients admitted to the ICU was very low. -Calorie and protein requirements were underestimated. -The mNUTRIC score can predict the energy intake of critically ill patients. -It is recommended to perform a complete nutritional assessment on the first day of hospitalization in order to correctly estimate energy needs.	STROBE: 22/22 / NOS: 8/9	2 +

(Continued)

10.3389/fnut.2022.1073782

TABLE 4 (Continued)

References	Design sample	Intervention tool used	Variables results	Results	Conclusions	Evaluation of the study report/Risk of bias	Level of evidence: SIGN
Zhang et al. (31). China.	Retrospective observational study. –136 patients admitted to different ICU's in China.	To investigate the applicability of mNUTRIC score to assess nutritional risks and predict outcomes of critically ill COVID-19 patients. / -mNUTRIC	–Medical data, mortality and complications of patients. -mNUTRIC score of nutritional risk.	-A large proportion of critically ill COVID-19 patients were at high nutritional risk on admission to the ICU. -Patients with high nutritional risk on ICU admission had significantly higher 28-day mortality in the ICU, as well as twice the likelihood of ICU death at 28 days (compared with those identified as having low nutritional risk).	-The mNUTRIC score may be a suitable tool for nutritional risk assessment and prognostic prediction in critically ill COVID-19 patients.	STROBE: 22/22 / NOS: 8/9	2 ++
Wang et al. (35). China.	Prospective observational study. –3107 critically ill patients admitted to the ICU.	-To identify nutritional risk in patients admitted to the ICU using the mNUTRIC score; and to describe the relationship between 28-day mortality and elevated nutritional screening scores. / -mNUTRIC	-mNUTRIC score. -Health-related variables (age, BMI, drug use, etc.) and mortality data. -Length of stay of patients in the ICU.	-Mortality at 28 days for the maximum mNUTRIC score was 67.4%. -The mNUTRIC score was an independent predictor of 28-day mortality, which increased by 8.5% for each point on the nutritional screening tool. -Higher mNUTRIC scores were associated with longer ICU stay.	-The mNUTRIC tool is a good tool for nutritional risk assessment in critically ill patients; it is practical and easy to use.	STROBE: 22/22 / NOS: 8/9	2 ++
Machado et al. (37). Brasil.	Prospective cohort study. –384 patients admitted to the ICU.	-To evaluate the performance of mNUTRIC, independently or combined with NRS 2002, in predicting hospital mortality in critically ill patients admitted to the ICU. / -mNUTRIC y NRS 2002.	-Nutritional screening -Length of hospital and ICU stay, in-hospital death, ICU readmission.	-Patients classified as nutritional risk according to mNUTRIC had a 3-fold higher risk of in-hospital mortality. -Patients classified as high nutritional risk according to NRS 2002 did not have a statistically significant increased risk of death. -Patients classified as nutritional risk by both tools had a 2-fold increased risk of in-hospital mortality.	-The NRS 2002 and mNUTRIC nutritional screening tools performed well as predictors of mortality, alone or in combination. -The mNUTRIC had better discriminative ability to quantify the risk of hospital mortality in critically ill patients.	STROBE: 20/22 / NOS: 9/9	2 +
Coruja et al. (3). Brasil.	Retrospective observational study. –208 patients admitted to the ICU.	- To compare the detection of nutritional risk by mNUTRIC and NRS 2002, to identify if they are concordant tools. -NRS 2002 y mNUTRIC	- mNUTRIC and NRS 2002 scores during the first 24 h after admission of patients to the ICU. -Prevalence of nutritional risk determined by screening tools.	-The most frequent component of the NRS 2002 was the severity of illness score. -The component most evaluated by mNUTRIC was the number of comorbidities. -There was fair concordance between the two nutritional risk screening tools.	- NRS 2002 and mNUTRIC identify nutritional risk differently, so the two instruments are proposed as not interchangeable.	STROBE: 21/22 / NOS: 7/9	2 +

(Continued)

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TABLE 4 (Continued)

References	Design sample	Intervention tool used	Variables results	Results	Conclusions	Evaluation of the study report/Risk of bias	Level of evidence: SIGN
Rattanachaiwong et al. (29). Israel.	Retrospective observational study. –120 patients admitted during the study period.	-To apply different nutritional assessment and screening tools (ASPEN and ESPEN criteria, NRS 2002 and mNUTRIC). -To compare these classifications with the SGA.	-Nutritional status. -Concordance of the different tools. -Mortality.	-NRS 2002 showed the highest sensitivity for identifying severe malnutrition. -NRS 2002, ASPEN and ESPEN criteria showed the highest specificity with GHS. -mNUTRIC had lower performance in detecting malnutrition.	-None of the tools showed an association with mortality after adjustment.	STROBE: 18/22 / NOS: 8/9	2 +
Cattani et al. (26). Brasil.	Systematic review. –36 selected articles that met the inclusion criteria.	-Summarize the evidence regarding the prevalence of nutritional risk and the predictive validity of the different nutritional risk screening instruments used in critically ill patients. / -Different screening tools found: mNUTRIC, NRS 2002, MUST, Nutritional Score Risk (NSR)	-Prevalence of nutritional risk -Predictive validity of nutritional screening tools.	-The mean prevalence of nutritional risk in critically ill patients was 55.9%. -The most commonly used instruments were the mNUTRIC and the NRS 2002. -Nutritional risk was an independent predictor of 28-day mortality.	- The prevalence of nutritional risk in critically ill patients varies widely. -Identification of patients at nutritional risk is not a simple task, but it is clinically relevant. -NRS 2002 and mNUTRIC could be the current tools available for nutritional risk assessment, due to their proven validity.	PRISMA: 26/27 / ROBIS: Low risk of bias.	1–
Liu et al. (28). China.	Randomized controlled trial. –220 patients admitted to the neurological ICU of a hospital in China.	-Individualized nutritional risk assessment and screening of the experimental group, with treatment prescription and review of the effects on the patients. / -NRS	-Incidence of pulmonary infection, hypoproteinemia, mechanical ventilation, hospitalization time, improvement and mortality rate.	-Nutritional assessment was able to diagnose malnutrition and establish correct nutritional support. -The number of patients at nutritional risk after therapy was reduced in the experimental group. -In the experimental group, the incidence of hypoproteinemia and pulmonary infection was reduced, hospitalization days were decreased, the rate of improvement of patients was increased and the mortality rate was decreased.	-Systematic nutritional assessment provided a theoretical basis for nutritional support in neurocritical patients. -The prognosis of patients who received individualized nutritional therapy was better.	CASPe: 9/11 / RoB: Low risk of bias.	1 +
Canales et al. (30). Estados Unidos.	Retrospective observational study. –312 patients admitted to the ICU.	-Compare mNUTRIC with NRS 2002 in terms of its relationship with macronutrient deficits in critically ill patients. / -mNUTRIC and NRS 2002	-Protein-calorie deficit. -Association with nutritional screening instruments.	-mNUTRIC scores are strongly associated with protein and calorie requirement; whereas no relationship was found between these requirements and NRS 2002.	-Larger studies are needed to validate the findings. -mNUTRIC is more closely matched to energy requirements than NRS 2002. -The use of these tools could improve clinical outcomes in patients at nutritional risk.	STROBE: 22/22 / NOS: 8/9	2 +

(Continued)

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TABLE 4 (Continued)

References	Design sample	Intervention tool used	Variables results	Results	Conclusions	Evaluation of the study report/Risk of bias	Level of evidence: SIGN
Gonzalez et al. (38). Brasil.	Prospective longitudinal observational study. –205 patients hospitalized in the ICU.	To compare the prognostic power of mNUTRIC and SGA, independently or simultaneously, to predict the risk of 28-day mortality following admission of critically ill patients. / -mNUTRIC and SGA.	-Nutritional screening by SGA and mNUTRIC (cut-off points). -Mortality risk -Number needed for screening (NNS).	-Patients classified as nutritional risk by mNUTRIC and as severely malnourished by SGA (SGA "C"), showed a risk of death after 28 days of ICU admission was more than 7 times higher, compared to patients without nutritional risk by mNUTRIC (regardless of nutritional status determined by SGA). -According to the NNS, one death could be averted for every 1.62 patients identified as being at nutritional risk by mNUTRIC score and classified as SGA "C" (severely malnourished).	-It is suggested that mNUTRIC be used in the first 24 h of ICU admission to detect patients at increased risk of mortality. -Subsequent nutritional assessment by SGA in patients classified as being at nutritional risk is associated with better identification of patients at increased risk of mortality and those in whom more aggressive nutritional therapy is recommended.	STROBE: 20/22 / NOS: 7/9	2 ++
Eslamian et al. (32). Irán.	Retrospective observational study. –150 patients hospitalized.	-To evaluate the association between intestinal permeability and nutritional status in a group of critically ill patients. / -NUTRIC and mNUTRIC.	-Intestinal markers related to intestinal permeability (zonulin and endotoxin). -Plasma glutamine levels. -NUTRIC and mNUTRIC scores.	–54% of patients were classified as high nutritional risk using mNUTRIC, while the proportion was 47% when NUTRIC was used. -Multivariate analyses showed significant associations between increased zonulin and endotoxin levels and increased NUTRIC or mNUTRIC category.	-Gut permeability-related levels are significantly positively associated with the nutritional risk tools used. -Physicians should evaluate critically ill patients with the NUTIC tool to assess nutritional risk, which may be associated with intestinal permeability.	STROBE: 19/22 / NOS: 7/9	2 +
Chourdakis et al. (33). Grecia.	Retrospective longitudinal observational study. –80 patients admitted to the ICU.	To translate and adapt the mNUTRIC score to the Greek language. To evaluate the predictive ability of mortality. / mNUTRIC.	–mNUTRIC score. -Prevalence of nutritional risk. -Mortality.	-The mNUTRIC tool was considered easy to use, fast and complete. -Cronbach's alpha was 0.58. -Increased mortality and comorbidities were observed among patients classified as high nutritional risk by mNUTRIC, compared with those at low nutritional risk.	-The Greek version of mNUTRIC was a validated, quick and easy to use tool; which is able to discriminate critically ill patients from benefiting from improved nutrition.	STROBE: 20/22 / NOS: 7/9	2 ++

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In addition, the latest ASPEN, ESPEN and Global Clinical Nutrition Community (GLIM) guidelines (40) determine that at least one phenotypic criterion and one etiological criterion must be available to make a diagnosis of malnutrition; thus, the parameters assessed by GHS can contribute to the development of this diagnosis.

In summary, the results found in this review can benefit the professional practice of nurses and patient outcomes, as they show how nurses are in charge of collecting information and determining nutritional risk using the screening tools analyzed (28, 31, 34, 36, 39). As we know, these tools are key for the prediction of mortality risk, complications or individual protein-energy adequacy. The ability to generate beneficial effects in patients has an impact on improving effectiveness and efficiency, since these tools can save costs and improve patient health outcomes (26, 42).

This study has some limitations. We are aware that observational studies may have more types of biases, such as the risk of selective reporting of the analysis and outcome, being one of the limitations of this study. In our review, most of the studies were not RCTs, and therefore it is recommended that studies with more robust designs [such as RCTs] be conducted to test the true scope of nutritional assessment tools in the health of critically ill patients. Another limitation of this study is the heterogeneity of the instruments found to screen for nutritional risk, since we have found various nutritional risk tools, and the possibility of using them or not depending on the context of the ICU of each hospital.

5. Conclusion

The nutritional assessment tools described were mNUTRIC, NRS 2002, NUTRIC, SGA, MUST and the ASPEN and ESPEN criteria. Among these tools, the most widely used and effective were mNUTRIC, NRS-2022 and SGA, either independently or in combination with each other.

The most highly rated tool with the best mortality prediction capacity was mNUTRIC. It was also the most useful for predicting the energy requirements of the patients, so that nutritional therapy could be established in those patients classified as high risk nutritional, with the aim of reducing comorbidity derived from malnutrition and reducing the length of stay of critical patients. Thus, among the tools for assessing nutritional risk, mNUTRIC was the most effective. SGA is a nutritional assessment tool that can complement and support the risk assessment performed by mNUTRIC.

Nutritional risk assessment and screening have been shown to be able to improve malnutrition and health status in critically ill patients. The use of any nutritional assessment tool on admission of critically ill patients is able to detect the risk of mortality, thus allowing earlier initiation of nutritional therapy to improve the prognosis of patients classified as high risk.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

VD-B, VG-C, EC-S, and RJ-V: conceptualization and software. VD-B, AM-S, VV-B, JS-G, and RJ-V: methodology. VD-B, VG-C, RJ-V, MC, and IS: validation. VD-B, VG-C, EC-S, and RJ-V: formal analysis. VD-B, VG-C, MC, and RJ-V: investigation. VD-B, AM-S, VV-B, JS-G, RJ-V, and MC: data curation and writing—original draft preparation. VD-B, VG-C, RJ-V, MC, and IS: writing—review and editing. VD-B: visualization and project administration. RJ-V and AM-S: supervision and funding acquisition. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Comorbidity and nutritional status in adult with advanced chronic kidney disease influence the decision-making choice of renal replacement therapy modality: A retrospective 5-year study

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Background: Nutritional and inflammation status are significant predictors of morbidity and mortality risk in advanced chronic kidney disease (ACKD). To date, there are a limited number of clinical studies on the influence of nutritional status in ACKD stages 4–5 on the choice of renal replacement therapy (RRT) modality.

Aim: This study aimed to examine relationships between comorbidity and nutritional and inflammatory status and the decision-making on the choice of RRT modalities in adults with ACKD.

Methods: A retrospective cross-sectional study was conducted on 211 patients with ACKD with stages 4–5 from 2016 to 2021. Comorbidity was assessed using the Charlson comorbidity index (CCI) according to severity (CCI: ≤ 3 and >3 points). Clinical and nutritional assessment was carried out by prognosis nutritional index (PNI), laboratory parameters [serum s-albumin, s-prealbumin, and C-reactive protein (s-CRP)], and anthropometric measurements. The initial decision-making of the different RRT modalities [(in-center, home-based hemodialysis (HD), and peritoneal dialysis (PD)] as well as the informed therapeutic options (conservative treatment of CKD or pre-dialysis living donor transplantation) were recorded. The sample was classified according to gender, time on follow-up in the ACKD unit (≤ 6 and >6 months), and the initial decision-making of RRT (in-center and home-RRT). Univariate and multivariate regression analyses were carried out for evaluating the independent predictors of home-based RRT.

Results: Of the 211 patients with ACKD, 47.4% (n=100) were in stage 5 CKD, mainly elderly men (65.4%). DM was the main etiology of CKD (22.7%) together with hypertension (96.6%) as a CV risk factor. Higher CCI scores were significantly found in men, and severe comorbidity with a CCI score>3 points was 99.1%. The mean time of follow-up time in the ACKD unit was 9.6±12.8 months. A significantly higher CCI was found in those patients with a follow-up time > 6 months, as well as higher mean values of eGFR, s-albumin, s-prealbumin, s-transferrin, and hemoglobin, and lower s-CRP than those with a follow-up <6 months (all, at least p<0.05). The mean PNI score was 38.9±5.5 points, and a PNI score≤39 points was found in 36.5%. S-albumin level>3.8 g/dl was found in 71.1% (n=150), and values of s-CRP≤1 mg/dl were 82.9% (n=175). PEW prevalence was 15.2%. The initial choice of RRT modality was higher in in-center HD (n=119 patients; 56.4%) than in home-based RRT (n=81;

40.5%). Patients who chose home-based RRT had significantly lower CCI scores and higher mean values of s-albumin, s-prealbumin, s-transferrin, hemoglobin, and eGFR and lower s-CRP than those who chose in-center RRT ($p<0.001$). Logistic regression demonstrated that s-albumin (OR: 0.147) and a follow-up time in the ACKD unit >6 months (OR: 0.440) were significantly associated with the likelihood of decision-making to choose a home-based RRT modality (all, at least $p<0.05$).

Conclusion: Regular monitoring and follow-up of sociodemographic factors, comorbidity, and nutritional and inflammatory status in a multidisciplinary ACKD unit significantly influenced decision-making on the choice of RRT modality and outcome in patients with non-dialysis ACKD.

KEYWORDS

advanced chronic kidney disease, comorbidity, Charlson comorbidity index, home-based renal replacement therapy, nutritional status, prognosis nutritional index, protein-energy wasting, renal replacement therapy

1. Introduction

Chronic kidney disease (CKD) has become a major public health problem due to its high incidence, prevalence, and associated morbidity and mortality (1). From the early stages of CKD and as the estimated glomerular filtration rate (eGFR) progresses, cardiovascular (CV) risk often increases exponentially and constitutes the leading cause of mortality in patients with CKD (2). Epidemiological data from the Global Burden of Disease Study 2017 (3) have shown that CKD is one of the leading causes of death in the last few years. The aging population and the increasing trend of CKD risk factors jointly contributed to more than half of CKD deaths. The main etiology of CKD varies according to the setting with high blood pressure (HBP), and diabetes mellitus (DM) being the most frequent causes of CV risk and adverse prognosis (1, 3).

The guidelines for CKD from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) (4) and the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (KDIGO) (5) recommend stage 4 and depending on the etiology and rate of progression of CKD, and close to stage 5 (eGFR: < 15 ml/min/1.73 m^2), it is mandatory to inform about the available therapeutic options including dialysis modalities. The educational approach is based on age, comorbidity, magnitude of proteinuria, and nutritional status among other clinical variables frequently assessed (5). There are usually different renal replacement therapy (RRT) modalities, including in-center hemodialysis (HD) and home-RRT [home-based HD, and peritoneal dialysis (PD)]. Other available therapeutic options in patients who choose not to start dialysis include conservative treatment of CKD and pre-dialysis living donor kidney transplantation. The K/DOQI guidelines (4) for the clinical evaluation, classification, and stratification of CKD recommend the assessment of the potential risks and benefits to make the most appropriate decision-making on when to start RRT.

Patients with advanced chronic kidney disease (ACKD) stage 4 or 5 have a severely decreased eGFR (<30 ml/min/1.73 m^2) and are therefore candidates for intensive monitoring and care in the specialized ACKD unit (6). Multidisciplinary ACKD units aim to provide comprehensive care to prevent and/or treat associated comorbidities and improve the quality of life at the end stages of CKD. The clinical approach consists of early referral to a specialized unit for the management and follow-up of CKD by a nephrologist, at least 6 months before the onset of RRT (7). Late referral of patients to ACKD units is associated with increased adverse outcomes and reduced long-term overall survival from all causes (8). Lack of prior information and/or education about available therapeutic options in CKD contributes to reduced use of home-RRT modalities or living donor kidney transplantation, as well as promoting unplanned and urgent initiation of dialysis (9, 10).

Nutritional disorders are significantly associated with morbidity and mortality in patients with ACKD and dialysis (11, 12). Causative factors such as lack of appetite and insufficient dietary intake of energy and protein due to the dietary restrictions of CKD, metabolic disturbances as well as metabolic acidosis, or the detrimental effects of the inflammatory state significantly increase the nutritional risk in patients with ACKD (12).

The prognostic nutritional index (PNI) score is a new composite indicator that includes a combination of serum albumin (s-albumin) and total lymphocyte count (TLC) (13). Previous studies (14–18) demonstrated that the PNI is related to poor clinical outcomes and predicts survival in a variety of solid tumors, postoperative complications, and other disease states. A cut-off point of the PNI score < 39 points has been recognized as an independent prognostic marker of clinical and mortality outcomes in older patients with CKD (19, 20) and patients with dialysis (21, 22).

In 2008 (23), the *International Society for Renal Nutrition and Metabolism (ISRNM)* proposed the term protein-energy wasting (PEW) syndrome in CKD as more than insufficient food intake, including disturbances in biochemical markers such as s-albumin, body composition, and the contribution of comorbidities and underlying inflammation. The diagnosis of PEW is based on several categories in which biochemical markers (e.g., s-albumin), body mass index (BMI), muscle mass, and dietary protein intake when accompanied by inflammation are usually modified (23). PEW is a common disorder estimated in 28–54% of patients with non-dialysis CKD (24). A retrospective cross-sectional study in 307 patients with CKD (11) showed that previous nutritional follow-up time, serum prealbumin (s-prealbumin), and right-handgrip strength were independent predictors of mortality risk at 10-year follow-up. Early identification of patients at nutritional risk and the use of nutritional screening tools (e.g., PNI score) together with a combination of several nutritional markers are necessary to decide to initiate nutritional support.

Identification and assessment of modifiable factors, such as nutritional risk and PEW, as well as the management of the most common comorbid conditions, may be clinically useful in preventing and/or avoiding underlying complications in end-stages of CKD. Consequently, it seems important to assess modifiable risk factors (i.e., nutritional and inflammatory status), together with CV risk factors (DM, hypertension) and underlying comorbidities, before informing patients with ACKD about available CKD therapeutic options or initiating RRT. Achieving or maintaining adequate nutritional status is one of the goals and challenges in ACKD stages 4–5, as well as at the time of choosing the RRT modality or before starting dialysis. This study aimed to examine relationships between comorbidity and nutritional and inflammatory status and the decision-making on the choice of RRT modalities in adult patients with ACKD.

2. Materials and methods

2.1. Study design and study population

A retrospective cross-sectional observational study was carried out at the Hospital Universitario La Princesa (Madrid, Spain). Data were collected retrospectively from December 2016 to December 2021 on adult patients with ACKD who attended the multidisciplinary ACKD unit in the last 5 years. Participants were required to meet the following inclusion criteria: adults (18 years or over) patients with CKD in stages 4–5 [eGFR: ≤ 20 ml/min/1.73 m^2] who choose any RRT modality [in-center (HD) and home-based (HD or peritoneal dialysis (PD)], conservative CKD treatment and pre-dialysis living donor transplant in the last 5 years at the ACKD unit. Patients with CKD stages 1–3b and those with an eGFR >30 ml/min/1.73 m^2 were excluded from this study.

According to the KDIGO guidelines (5) is recommended to refer patients with eGFR <30 ml/min/1.73 m^2 (eGFR stages: G4–G5) to a nephrologist specializing in ACKD, and to initiate information and education on RRT modalities and available treatment options.

This study was approved by the Ethics Committee of Hospital Universitario de La Princesa and was conducted according to the guidelines of the Declaration of Helsinki (Code number: 4247).

2.2. Data collection

The data collected and selected for the study coincided with the scheduled visit to inform about the different modalities of RRT (in-center, home-based HD, and PD) and informed therapeutic options available (conservative treatment of CKD or pre-dialysis living donor transplantation), within the framework of the clinical and care protocol of the ACKD unit.

The estimated glomerular filtration rate (eGFR) was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) using the 2021 CKD-EPI Creatinine equation (25). The eGFR was classified according to the KDIGO clinical practice guidelines for the evaluation and management of CKD (5).

Sociodemographic data, laboratory parameters, and most frequent comorbidities were collected retrospectively from the medical record of each participant. The date of admission and discharge was retrospectively registered to define the mean follow-up time at the ACKD unit in the last 5 years. The sample was classified according to the median follow-up time using a cut-off point of 6 months to assess the influence of nutritional and inflammatory status as well as underlying comorbidities on clinical outcomes.

2.3. Assessment of comorbidity

The comorbidity was assessed using the modified Charlson comorbidity index (CCI) score (26). It consists of 19 items that include the most frequent pathologies or comorbid conditions and adds one point for each decade in patients aged 50 years and older. The sum of the CCI items classifies comorbidity as follows: no comorbidity (0 points), low comorbidity (1–2 points), and severe comorbidity (≥ 3 points) (26).

Blood pressure (BP) was measured using an automatic blood pressure monitor (OMROM®; M6; Netherlands, EU). The mean BP values corresponding to the three different measurements were recorded to improve the reproducibility of BP measurements as a standard procedure in the clinical practice of the multidisciplinary ACKD unit every 3 months coinciding with the scheduled medical visit. The mean blood pressure collected in this study coincides with the BP measured during the medical visit in which the RRT modalities. HBP was defined as systolic and diastolic BP ≥ 140/90 mmHg and was considered a CV risk factor (27).

2.4. Laboratory parameters

Biochemical and hematological parameters were retrospectively collected from medical records for all participants before choosing the RRT modality or therapeutic election. S-albumin (g/dl), s-prealbumin (mg/dl), serum transferrin (s-transferrin; mg/dl), and serum C-reactive protein (s-CRP; mg/dl), hemoglobin (Hb), and TLC concentrations were analyzed by automated standardized methods in the laboratory of the Hospital Universitario de La Princesa. All parameters were analyzed by the standard clinical protocol of the ACKD unit.

2.5. Assessment of nutritional and inflammatory status

The prognostic nutritional index (PNI) is a novel score that has previously been used under several disease conditions and patients with CKD (14–20). The PNI score was calculated as follows: [10 × serum albumin (g/dl) + (0.005 × total lymphocyte count (cells x 10^3 mm^3] (13). According to previously published studies (19, 20) and mean PNI values in the sample, the cut-off point of the PNI score was set at 39 points. Patients were classified into two groups according to the PNI score cut-off point as follows: nutritional risk (PNI: ≤ 39 points) and no nutritional risk (PNI: >39 points). Levels of the s-albumin <3.8 g/dl and s-CRP >1 mg/dl were used according to the criteria proposed by the ISRNM together with the PNI score to define nutritional risk and PEW (23).

As part of the standard management and care of patients with ACKD, nutritional status is assessed and monitored every 3 months at scheduled visits by a renal dietitian-nutritionist, or more frequently as required by the patient in the ACKD unit. Patients with ACKD receive regular and individualized nutritional counseling and medical follow-up. Protein intake of 0.6–0.8 g/kg/day is recommended in patients with diabetic CKD and 0.5–0.6 g/kg/day in patients with non-diabetic CKD, together with a salt-free diet and low potassium and phosphorus intake

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(28). An individualized energy intake between 25 and 35 kcal/kg/day based on age, gender, physical activity level, body composition, weight goals, CKD stage, and concurrent comorbidities or the presence of inflammation or other metabolic disturbances is usually recommended to achieve and/or maintain adequate nutritional status according to KDOQI Guidelines on Nutrition (28). Nutritional recommendations and the individualized diet are personalized according to the stage of CKD, laboratory parameters, and the patient's progress at each of the scheduled medical visits. Nutritional management is usually carried out in collaboration with a multidisciplinary team (a nephrologist, a nurse specializing in Nephrology, and a dietitian–nutritionist).

2.6. Statistical analysis

The sample size was calculated using the statistical program G. Power version 3.1.9.4 (Franz Faul, Universitat Kiel, Germany) with a power of 90% and a significance level of 5%. The study required a sample size of 137 subjects to detect significant interactions with the RRT modality. The effect size was calculated using Cohen's *d*-value according to RRT modality (in-center or home-based) and the mean age of each group. Cohen's *d*-value was 0.723, and the calculated effect size was 0.345. Data are expressed as mean ± standard deviation and as frequencies or percentages according to the nature of the variable analyzed. To compare the frequency and mean differences, *p*-values were calculated using Chi-square and Fisher's exact test for categorical variables and Student's *t*-test or the non-parametric Mann–Whitney U-test for continuous variables. Pearson's Chi-square parametric correlations were examined to assess the strength of the association between the variables. Univariate and multivariate logistic regression analyses were used, and the corresponding odds ratio (OR) and 95% confidence interval (95%CI) were calculated. In-center and home-based dialysis modalities were used as the dependent and dichotomized variables in the univariate and multivariate regression analyses. Only data from the univariate analysis that had a value of *p* of 0.10 or less were tested *a priori* to explore possible changes in the response variable during multiple logistic regression analysis. A binary logistic regression model using the forward stepwise conditional method was used. The Statistical Package for Social Science (SPPS for Windows) version 23.0 was used in all statistical analyses. A value of *p* of <0.05 was considered statistically significant.

3. Results

3.1. General characteristics of the study population and classification according to gender

Table 1 summarizes clinical and biochemical parameters characteristics in the study population and according to gender. Of the 211 patients with ACKD, 138 patients with CKD were men (65.4%), mainly older than women ($p = 0.020$). A higher men proportion were living with a family, had a university education, and were active workers (Table 1). The mean value of eGFR was 13.7 ± 3.4 ml/min/1.73 m^2. According to the eGFR staging, 52.6% ($n = 111$) were in stage 4 CKD and 47.4% ($n = 100$) were in stage 5 CKD. In CKD stage 4, 68.4% ($n = 76$) were men, while in CKD stage 5, 62.0% ($n = 62$) were men. Mean eGFR values did not differ significantly between men and women ($p = 0.183$).

TABLE 1 Clinical and biochemical parameters characteristics of 211 participants in the study and by gender.

Variables	Total (n=211)	Male (n=138)	Female (n=73)
Age (years)	71.7 ± 12.8	73.6 ± 11.2	68.1 ± 15.0
Living with a family *n* (%)	138 (65.4)	105 (76.1)	33 (45.2)
Active workers *n* (%)	65 (30.8)	40 (28.9)	25 (34.2)
University education *n* (%)	73 (34.6)	50 (36.2)	23 (31.5)
eGFR (mL/min/1.73 m^2)*	13.7 ± 3.4	14.0 ± 3.5	13.3 ± 3.1
CCI (points) CCI: ≤ 3 points *n* (%) CCI: >3 points *n* (%)	6.5 ± 1.3 2 (0.9) 209 (99.1)	6.8 ± 1.1 1 (0.7) 137 (99.2)	6.1 ± 1.4 1 (1.3) 72 (98.6)
DM *n* (%)	48 (22.7)	32 (23.1)	16 (21.9)
High blood pressure *n* (%)	204 (96.6)	132 (95.6)	72 (98.6)
Time on follow-up in ACKD unit (months)	9.6 ± 12.8	9.2 ± 12.3	10.3 ± 13.7
s-Albumin (g/dl)	3.8 ± 0.5	3.9 ± 0.5	3.8 ± 0.5
s-Prealbumin (mg/dl)	28.9 ± 5.1	29.0 ± 5.4	28.7 ± 4.3
s-Transferrin (mg/dl)	200.4 ± 49.1	198.7 ± 42.1	203.6 ± 60.5
s-CRP (mg/dl)	0.5 ± 1.1	0.6 ± 1.2	0.5 ± 0.9
Hemoglobin (g/dl)	11.2 ± 1.23	11.2 ± 1.2	11.2 ± 1.1
Total lymphocyte count (10^3/mm^3)	2,035 ± 0.4	2,065 ± 0.4	1,978 ± 0.4
PNI (points)	38.9 ± 5.5	38.8 ± 5.7	39.1 ± 5.2

CCI, Charlson comorbidity index; PNI, prognostic nutritional index; s-CRP, serum C-reactive protein. *eGFR, estimated glomerular filtrate rate was measured by the 2021 CKD-EPI equation (25).

Mean CCI score values were 6.5 ± 1.3 points, with significantly higher scores found in men (6.8 ± 1.1 points) than in women (6.1 ± 1.4 points; $p < 0.001$). Analyzing the CCI score, 99.10% ($n = 209$) had severe comorbidity (CCI: > 3 points), while only two patients with ACKD (0.9%) had low comorbidity (CCI: ≤ 3 points). DM was the main diagnosed cause leading to CKD in 22.7% ($n = 48$). HBP accounted for 96.6% ($n = 204$) and was significantly more frequent in men ($n = 132$; 95.6%) than in women ($n = 72$; 98.6%). Other commonly associated comorbidities were peripheral vascular disease and cerebrovascular disease. The mean time of medical follow-up in the ACKD unit was 9.6 ± 12.8 months with no significant differences between men and women ($p = 0.56$; Table 1).

Mean s-albumin values were 3.8 ± 0.5 g/dl without significant differences between gender. The cut-off point of s-albumin level > 3.8 g/dl was found in 71.1% ($n = 150$) of patients with ACKD, more often in men (45.5%; $n = 54$) than in women (25.6%; $n = 54$; $p = 0.30$; data not shown). Mean values of s-CRP were 0.5 ± 1.1 mg/dl without non-significant differences between gender ($p = 0.66$). Values of s-CRP ≤ 1 mg/dl were found in 175 patients with ACKD (82.9%) in a similar way in men (82.6%) than in women (83.6%; $p = 0.51$; data not shown). The conjoint use of the cut-off points of s-albumin <3.8 g/dl and s-CRP ≥ 1 mg/dl was found in 15.2% ($n = 32$) as PEW markers, being more frequent in men (10.4%; $n = 22$). No significant differences were found with biochemical markers such as s-prealbumin, s-transferrin, or hematological parameters (hemoglobin, TLC) between both groups (Table 1).

The mean PNI score was 38.9 ± 5.5 points and was found to be similar between men (PNI: 38.8 ± 5.7 points) and women (PNI: 39.1 ± 5.2 points)

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subjects ($p = 0.707$). A cut-off point of PNI ≤ 39 points was found in 77 adults with ACKD (36.5%) with a non-significant higher frequency in the male group than in the female group (68.8 vs. 32.2%; $p = 0.45$; Table 1).

3.2. Comparison of clinical and biochemical parameters characteristics in the study according to the previous follow-up time in the advanced chronic kidney disease unit

Table 2 shows the results according to follow-up time in the ACKD unit. The median follow-up time was 6 months (r: 1–64 months). No significant differences were found with gender, living with a family, having university studies, and being an active worker with the follow-up time in the ACKD unit (Table 2). Patients with ACKD on follow-up time > 6 months accounted for 42.1% ($n = 89$). Higher CCI was significantly found in those patients with follow-up time > 6 months (CCI score: 7.1 ± 1.1 points) than those who had a follow-up time ≤ 6 months (CCI: 6.3 ± 1.3 points; $p = 0.024$). CCI score was >3 points in more than 98.0% of patients with ACKD follow-up in the ACKD unit. No differences were found in patients with diabetic and hypertensive ACKD according to the previous follow-up time. Notably, patients with regular follow-up for more than 6 months had significantly higher mean values of eGFR, s-albumin, s-prealbumin, s-transferrin, and hemoglobin, and lower levels of s-CRP than those with follow-up ≤6 months ($p < 0.001$). Mean PNI values were significantly higher in patients with ACKD with follow-up time > 6 months (Table 2). Only 13 patients with ACKD (18.8%) with a follow-up time > 6 months had a PNI score ≤ 39 points compared with those with follow-up time in the ACKD unit ≤6 months (81.2%; $n = 53$; $p < 0.001$; data not shown).

TABLE 2 Comparison of clinical and biochemical parameters of 211 participants in the study according to the time on follow-up in the ACKD unit.

Variables	No follow-up ACKD unit ≤6 months (n=122)	Follow-up ACKD unit >6 months (n=89)	p-Value
Age (years)	67.6 ± 14.5	72.7 ± 12.3	0.050
Male n (%)	83 (68.0)	55 (61.7)	0.381
Female n (%)	39 (31.9)	34 (38.2)	
Living with a family n (%)	60 (49.1)	61 (68.5)	0.600
Active workers n (%)	23 (18.8)	30 (33.7)	0.565
University education n (%)	33 (27.0)	34 (38.2)	0.970
eGFR (mL/min/1.73 m^2)*	12.8 ± 3.7	15.2 ± 2.3	<0.001
CCI (points) CCI: ≤ 3 points n (%) CCI: >3 points n (%)	6.3 ± 1.5 2 (1.6) 120 (98.3)	7.09 ± 1.1 0 89 (100%)	0.024
DM n (%)	28 (58.3)	20 (41.6)	0.991
High blood pressure n (%)	118 (96.7)	86 (96.6)	0.971
s-Albumin (g/dl)	3.7 ± 0.6	4.0 ± 0.4	0.002
s-Prealbumin (mg/dl)	27.5 ± 5.3	30.7 ± 4.1	<0.001
s-Transferrin (mg/dl)	188.3 ± 50.3	217.0 ± 42.5	<0.001
s-CRP (mg/dl)	0.8 ± 1.4	0.2 ± 0.3	<0.001
Hemoglobin (g/dl)	10.9 ± 1.4	11.6 ± 0.9	<0.001
Total lymphocyte count (10^3/mm^3)	2,064 ± 0.4	1,995 ± 0.4	0.296
PNI (points)	37.9 ± 6.0	40.3 ± 4.4	<0.001

ACKD, advanced chronic kidney disease. CCI, Charlson comorbidity index; PNI, prognostic nutritional index; s-CRP, C-reactive protein. *eGFR, estimated glomerular filtrate rate was measured by the 2021 CKD-EPI equation (25).

3.3. Assessment of demographic, comorbidity, and biochemical parameters of the study population about the initial decision-making choice of in-center or home-based renal replacement therapy

Table 3 shows the comparison of clinical and biochemical parameters according to the free decision-making and initial choice of RRT. The initial choice of RRT modality was in-center HD ($n = 119$ patients; 56.4%) and home-based RRT ($n = 81$; 40.5%) in both home HD and PD modalities. Home-based HD accounts for 4.3%. Regarding the election of PD techniques, 44 patients (61.0%) chose continuous ambulatory PD and 28 patients with ACKD (38.8%) chose automated nocturnal peritoneal dialysis. Conservative treatment of CKD accounted for 4.3% ($n = 9$ patients), whereas pre-dialysis living donor transplantation was 0.9% ($n = 2$ patients).

In-center RRT was chosen by patients with older, less occupationally active ACKD, with less university education and a mean CCI score of 6.9 ± 1.1 points ($p < 0.001$). Patients who chose home-based RRT had significantly lower CCI scores than those who chose in-center RRT ($p < 0.001$). In addition, patients who chose home-RRT had also significantly higher mean values of s-albumin, s-prealbumin, s-transferrin, hemoglobin, and eGFR and lower s-CRP than those who chose in-center RRT ($p < 0.001$). No significant differences were found with TLC between both groups ($p = 0.79$; Table 3).

3.4. Univariate and multivariate regression analyses

Table 4 shows the factors associated with the likelihood of choosing in-center or home-based RRT using a univariate binary regression analysis. Sociodemographic factors such as age, being active workers, and university education were significantly related to both in-center or home-based RRT choices. Higher levels of eGFR, s-albumin, s-prealbumin, s-transferrin, hemoglobin, and follow-up time in the ACKD unit >6 months were also significantly and independently associated with the free decision-making to choose in-center and home-based RRT modality (Table 4).

Multivariate binary logistic regression showed that well-known predictors such as s-albumin (OR: 0.147; 95% CI: 0.057–0.378) and follow-up time in the ACKD unit for >6 months (OR: 0.440; 95% CI: 0.204–0.950) were significantly related to the probability of choosing home-based RRT (all at least, $p < 0.05$), while age (OR: 1.570; 95% CI: 1.009–1.108) and CCI score (OR: 1.986; 95% CI: 1.251–3.154) were inversely associated with the probability of choosing home-based RRT (Table 5).

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TABLE 3 Comparison of clinical and biochemical parameters of 211 participants in the study according to the decision-making choice of home-based or in-center renal replacement therapy.

Variables	In-center RRT (*n*=119)	Home-based RRT (*n*=81)	*p*-Value
Age (years)	74.9 ± 14.4	65.4 ± 11.3	<0.001
Gender Male *n* (%) Female *n* (%)	 79 (66.3) 40 (33.6)	 53 (65.4) 28 (34.5)	0.889
Living with a family *n* (%)	70 (58.8)	58 (71.6)	0.098
Active workers *n* (%)	17 (14.3)	46 (56.8)	<0.001
University education *n* (%)	19 (15.9)	53 (59.6)	<0.001
eGFR (mL/min/1.73 m^2)*	13.1 ± 3.7	14.6 ± 2.9	0.013
CCI (points) CCI: < 3 points *n* (%) CCI: ≥ 3 points *n* (%)	6.9 ± 1.5 0 119 (100)	5.8 ± 11.1 2 (2.4) 79 (97.5)	0.163
DM *n* (%)	34 (70.3)	14 (29.1)	0.990
High blood pressure *n* (%)	117 (98.3)	77 (95.0)	0.225
Time on follow-up in ACKD unit (months)	8.2 ± 12.6	11.1 ± 12.8	0.128
s-Albumin (mg/dl)	3.7 ± 0.5	4.2 ± 0.4	<0.001
s-Prealbumin (mg/dl)	27.3 ± 4.0	31.6 ± 5.6	<0.001
s-Transferrin (mg/dl)	191.1 ± 52.2	218.2 ± 39.9	<0.001
s-CRP (mg/dl)	0.8 ± 1.4	0.2 ± 0.5	<0.001
Hemoglobin (g/dl)	10.8 ± 1.2	11.9 ± 1.0	<0.001
Total lymphocyte count (10^3/mm^3)	2,099.0 ± 0.4	1,947.0 ± 0.4	0.795
PNI (points)	37.2 ± 5.3	41.8 ± 4.5	<0.001

CCI, Charlson comorbidity index; s-CRP, C-reactive protein; PNI, prognostic nutritional index. *eGFR, estimated glomerular filtrate rate was measured by the 2021 CKD-EPI equation (25).

TABLE 4 Univariate binary regression analysis of factors associated with the decision-making to choose in-center or home-based renal replacement therapy.

Variable	In-center RRT OR beside (95% CI)	*p*-Value	Home-based RRT OR beside (95% CI)	*p*-Value
Age (years)	1.093 (1.060–1.128)	<0.001	1.095 (1.061–1.130)	<0.001
Gender (Male)	0.929 (0.512–1.685)	0.800	0.874 (0.483–1.583)	0.657
Living with a family (%)	0.531 (0.288–0.977)	0.042	0.567 (0.309–1.038)	0.066
Active workers (%)	0.089 (0.042–0.188)	<0.001	0.086 (0.041–0.182)	<0.001
University education (%)	0.095 (0.005–0.188)	<0.001	0.100 (0.051–0.196)	<0.001
eGFR (mL/min/1.73 m^2)*	0.923 (0.848–1.004)	0.062	0.916 (0.841–0.997)	0.043
CCI (points)	2.973 (2.093–4.224)	<0.001	3.016 (2.117–4.297)	<0.001
Follow-up ACKD unit ≥6 months	0.807 (0.437–1.488)	0.492	0.539 (0.303–0.959)	0.036
s-Albumin (g/dl)	0.134 (0.062–0.291)	<0.001	0.107 (0.047–0.242)	<0.001
s-Prealbumin (mg/dl)	0.818 (0.756–0.884)	<0.001	0.819 (0.757–0.885)	<0.001
s-Transferrin (mg/dl)	0.989 (0.981–0.995)	<0.001	0.988 (0.982–0.995)	<0.001
s-CRP (mg/dl)	2.548 (1.434–4.526)	<0.001	2.603 (1.459–4.644)	<0.001
Hemoglobin (g/dl)	0.476 (0.346–0.654)	<0.001	0.476 (0.347–0.653)	<0.001
Total lymphocyte count (10^3/mm^3)	1.936 (1.038–3.612)	0.038	1.993 (1.068–3.719)	0.030
PNI (points)	1.229 (1.131–1.328)	<0.001	2.747 (1.500–5.032)	<0.001

CCI, Charlson comorbidity index; PNI, prognostic nutritional index; s-CRP, serum C-reactive protein. *eGFR, estimated glomerular filtrate rate was measured by the 2021 CKD-EPI equation (25).

4. Discussion

Study results demonstrate that certain sociodemographic factors (advanced age, living with a family, being an active worker and university education, as well as previous follow-up time in a multidisciplinary ACKD unit, and regular nutritional monitoring) with comorbidity status influenced the initial decision-making choice of RRT modality before starting dialysis in adults with ACKD stages 4–5. In this sample, patients with ACKD were older adults, were more often men, and were mainly in CKD stage 5 (62.0%). DM was the main etiology leading to CKD (22.7%) along with hypertension, which accounted for 96.6% were the most prevalent comorbidities found in patients with ACKD (Table 1).

Comorbidity as measured by CCI is associated with adverse outcomes and is a strong predictor of mortality in patients with dialysis (29, 30). A Canadian study of 530,771 patients with CKD highlighted that a higher degree of comorbidity was associated with worse outcomes, such as hospitalization, a longer length of hospital stay, and all-cause mortality (31). To date, there is a lack of studies on how comorbidity influences the decision-making choice of RRT modalities in adults with ACKD before starting dialysis. In this study, severe comorbidity significantly accounted for 99.1% of patients with ACKD. In fact, univariate and multivariate regression analyses significantly showed that the CCI score was inversely related to the probability of choosing home-based RRT. Due to the importance and complexity of this decision-making process, the importance of the multidisciplinary team is essential to support patients in their diagnosis and the complex decision about the initiation of dialysis (32).

Assessment and medical follow-up of underlying comorbidities related to CKD help to individualize and improve care in the setting of multidisciplinary ACKD units (33). In this study, it should be noted that a follow-up time > 6 months in the ACKD unit significantly improved eGFR, visceral protein profile (s-albumin, s-prealbumin, s-transferrin), s-CRP concentration, and mean hemoglobin levels in multimorbidity patients with ACKD (Table 2). A comprehensive clinical approach together with a follow-up time of >6 months significantly improved

TABLE 5 Multivariate binary regression analysis of factors associated with the decision-making to choose home-based renal replacement therapy.

Variable	OR (95% CI)	Value of p
Age (years)	1.570 (1.009–1.108)	0.020
CCI (points)	1.986 (1.251–3.154)	0.004
Follow-up at ACKD unit >6 months	0.440 (0.204–0.950)	0.036
s-Albumin (g/dl)	0.147 (0.057–0.378)	<0.001

ACKD, advanced chronic kidney disease; CCI, Charlson comorbidity index.

clinical outcomes as has been shown in the univariate and multivariate regression analyses of the study (Tables 4 and 5). Current strategies for the management of adults with ACKD indicate that a coordinated approach and intervention on modifiable risk factors through integrated and specialized care in the ACKD unit delays the progression of CKD and prevents complications and comorbidities before the onset of RRT (32, 34). The presence of specialized care programs before initiating dialysis and early education has been associated with increased adherence to treatment and dietary prescription (35). These assumptions mentioned earlier hold in the management of patients with ACKD, which increases the incidence of patient choice of home-RRT modalities and improves patients' perception of autonomy (35, 36). Unscheduled initiation of dialysis and patients' choice of initial RRT modality may also affect patients' experiences and clinical outcomes (6, 33). Patients who are not referred early enough to a multidisciplinary nephrology team-led follow-up program, and unscheduled initiation of dialysis, are associated with increased morbidity and decreased survival in any RRT technique (9, 10).

Nutritional disorders are a common condition in ACKD associated with multimorbidity and worse survival outcomes (12). The PNI score is an indicator of immune and nutritional status that has been shown as an independent predictive risk factor in different disease conditions (14–18) as well as in older patients with ACKD (19, 20). A case–control study in older patients with ACKD stages 4–5 demonstrates that the median PNI score value was 48.37 points in an elderly Mediterranean cohort of patients with ACKD who had an adequate nutritional status when compared to age-sex matched with their controls (20). A PNI score < 39 points was a significant predictor of nutritional risk in patients with CKD stages 3–4 and has been associated with the early onset of RRT and an increased mortality rate (19). In this study, a PNI score ≤ 39 points as an indicator of nutritional risk was found in 36.5% of patients with ACKD stages 4–5, as well as a risk factor in the choice of RRT modality in the univariate analysis, in line with previously published studies (19, 20).

Protein-energy wasting is related to mild to moderate inflammatory states, favoring the progression of CKD and even accelerating early entry into RRT. S-albumin and s-CRP are well-known risk factors for morbidity and mortality in both patients with CKD and dialysis (11, 37, 38). In addition to the PNI risk score, PEW was measured using a combination of two biochemical markers s-albumin and s-CRP in agreement with ISRNM proposed PEW diagnosis criteria (23). It is noteworthy that the mean values of s-albumin and s-CRP in this study were following the normal ranges. Mostly, s-albumin level > 3.8 g/dl was found in 71.1% of the sample, while s-CRP ≤ 1 mg/dl was present in 175 patients with ACKD (82.9%; data not shown). In this study, s-albumin and s-CRP were significantly associated in the univariate analysis with the likelihood of choosing a home-based RRT (Table 4). However, in the multivariate regression analysis, only s-albumin was significantly related to the likelihood of choosing home-RRT (OR: 0.14; CI95%: 0.057–0.378; $p < 0.001$; Table 5). PEW prevalence measured by both biomarkers (s-albumin and s-CRP) was 15.1%. These results show a lower prevalence of PEW when compared with a previously published meta-analysis (24) in which PEW was 28–54% of patients with CKD. The possible divergence of results between the PNI score and the combination of PEW markers employed is partially linked to the sensitivity and cut-off points of the markers used, as well as the high mean s-albumin levels and low degree of inflammation found in this sample.

The KDIGO Clinical Guidelines (5) recommend initiating an informed scheme on the different RRT modalities and therapeutic options available in patients with stage 4 CKD. In the current study, the different modalities of RRT (in-center, home-based) along with other therapeutic options (conservative treatment of CKD and living donor transplantation in pre-dialysis) are usually informed by a nurse specialized in nephrology in the framework of standard care at the ACKD unit. Data results from this study showed that the initial decision-making choice was higher in-center RRT compared with home-based RRT modalities (Table 3), whereas conservative CKD treatment and pre-dialysis living donor transplantation were in both <5% in the sample. Patients with ACKD who chose home-RRT were mainly younger male subjects, more labor-active, with a higher level of university education and a lower degree of comorbidity compared to in-center RRT. Moreover, patients with ACKD who chose in-center RRT had significantly higher mean values of s-albumin, s-prealbumin, s-transferrin, and hemoglobin concentrations, as well as a lower degree of inflammation, as measured by mean s-CRP levels (Table 3). Nutritional risk measured by PNI score was significantly lower in patients who chose home-based RRT (18.8%) compared with in-center RRT (81.2%). Conversely, older age, s-CRP, and PNI scores ≤39 points were significant independent predictors in the univariate analysis for decision-making in-center and home-based RRT choices in adults with ACKD. Furthermore, follow-up time > 6 months, higher eGFR, and improvement of s-albumin, s-prealbumin, s-transferrin, and levels of hemoglobin concentrations (at least, $p < 0.05$) were also significantly associated with free decision-making of RRT (Table 4). These results are relevant from the perspective that clinical outcomes influence the patient's decision to choose a home-based RRT modality. In addition, home-based RRT has been shown to have a positive impact on patient autonomy, quality of life, and health system costs (39, 40). Previous studies (32, 36) reported that patients with home-based RRT maintained independence and autonomy to work or study full-time as has been shown in the current study, and had also a better quality of life than those receiving HD at the center.

This study has some strengths and weaknesses that should be taken into account. This cross-sectional study is limited by the fact that it was conducted in a single ACKD unit, and the majority were older with a high prevalence of DM and severe comorbidity. Consequently, the results cannot be generalized to patients with early stages of CKD or in dialysis. However, the sample size of this study is relatively large. To the best of our knowledge, this is one of the few published studies that jointly assess the influence of comorbidity and nutritional status on the decision-making of choice of RRT modalities. By contrast, ISRNM protein-energy wasting criteria is a criterion to be assessed in future. Given the retrospective nature of the study, certain variables such as iron and lipid profiles, usual

pharmacological treatment, dietary intake, body composition measurements, or quality of life before initiating any RRT modality were not recorded. Based on the earlier results, further longitudinal studies assessing the quality of life and mortality of adults with ACKD after admission to RRT seem relevant for future research.

5. Conclusion

In conclusion, regular monitoring and follow-up of sociodemographic factors, comorbidity, and nutritional and inflammatory status in a multidisciplinary ACKD unit significantly influenced decision-making on the choice of RRT modality in patients with non-dialysis ACKD. Early referral and follow-up >6 months in the ACKD unit improves clinical outcomes. Nutritional monitoring and follow-up of the patient together with underlying comorbidities help to identify and/or prevent potential CKD-related risk factors and to plan in advance nutritional intervention strategies before starting RRT. Further studies are required to evaluate longitudinally the impact of multimorbidity, nutritional, and inflammatory status on CKD progression.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Ethics Committee of the Hospital Universitario de La Princesa, (Madrid, Spain) with code number: 4247. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

GÁ-G and GB developed the study design and methodology, research and data collection. ÁN, MC, and GÁ-G carried out the main analysis with supervision from GB and CB. In addition, GÁ-G and MR wrote the first and final drafts of the manuscript. GB, CB, MA, CG, AT, and MR made important critical revisions. Each author contributed important intellectual content during manuscript drafting. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic performance of the NRS2002, NUTRIC, and modified NUTRIC to identify high nutritional risk in severe acute pancreatitis patients

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Background: Acute pancreatitis (AP) is the most common gastrointestinal disease requiring hospital admission. AP patients are categorized as mild, moderately severe, and severe AP (SAP). For SAP patients, malnutrition increases susceptibility to infection and mortality. The Nutritional Risk Screening 2002 (NRS 2002), the Nutrition Risk in Critically Ill (NUTRIC) score and modified Nutrition Risk in Critically Ill (mNUTRIC) are nutritional risk screening tools of critically ill patients and have not been validated in patients with SAP. It is essential to evaluate the prognostic performance of these nutritional risk screening tools.

Materials and methods: A retrospective study was designed to validate the NRS 2002, NUTRIC, and mNUTRIC when applied to SAP patients. Receiver operating characteristic curves were plotted to investigate the predictive ability of clinical outcomes by comparing areas under the curve (AUC). Appropriate cut-offs were calculated by using Youden's index. Patients were identified as being at high nutritional risk according to the calculated cut-off values. The effects of different scoring systems on mortalities were calculated using the Cox proportional hazards model. Logistic regression was used to assess the association between the energy provision and 28-day mortality.

Results: From January 2013 to December 2019, 234 SAP patients were included and analyzed. Patients categorized as high nutritional risk by the NRS 2002 (12.6% versus 1.9% for 28-day and 20.5% versus 3.7% for 90-day), NUTRIC (16.2% versus 0.0% for 28-day and 27.0% versus 0.0% for 90-day), and mNUTRIC (16.4% versus 0.0% for 28-day and 26.4% versus 0.8% for 90-day) had significant higher mortality than those categorized as low nutritional risk. The NUTRIC (AUC: 0.861 for 28-day mortality and 0.871 for 90-day mortality, both cut-off value ≥3) and mNUTRIC (AUC: 0.838 for 28-day and 0.828 for 90-day mortality, both cut-off value ≥3) showed better predictive ability of the 28- and 90-day mortality than the NRS 2002 (AUC: 0.706 for 28-day mortality and 0.695 for 90-day mortality, both cut-off value ≥5).

Conclusion: The NRS 2002, NUTRIC, and mNUTRIC scores were predictors for the 28- and 90-day mortalities. The NUTRIC and mNUTRIC showed better predictive ability compared with the NRS 2002 when applied to SAP patients.

KEYWORDS

severe acute pancreatitis, NRS 2002, NUTRIC score, mNUTRIC score, nutritional risk, intensive care unit, mortality risk

Introduction

According to the 2012 updated revision of Atlanta Classification of acute pancreatitis (AP) (1), mild AP is the most common form with no organ failure, local or systemic complications and usually can be resolved in the first week. Most patients with mild AP are self-limited, achieving full recovery in less than a week (2, 3). Unfortunately, unlike mild AP, moderately severe, and severe AP (SAP) have rather high mortality (4, 5). SAP is defined by persistent organ failure, that is, organ failure >48 h. In patients with SAP, the oral route is often not feasible, there is inadequate nutritional supplementation, and a protein deficiency will occur after the first week of hospitalization (6). Artificial nutrition is an important treatment in patients with SAP, and many patients with SAP have suffered worse outcomes due to inadequate nutritional supplementation. It has been established that this type of patient presents a marked inflammatory response, as well as one of the highest catabolic rates, regardless of the nutritional status before the onset of the disease (7). To such descriptions, in these patients there is a significant negative impact on the nutritional status and therefore should be considered a high nutritional risk. Therefore, early identification of patients at high nutritional risk and appropriate nutrition support is very important to improving outcomes resulting from the treatment of SAP and the patient's quality of life (8).

The present ESPEN guidelines state that patients with SAP should be considered at high nutritional risk because of the catabolic nature of the disease and the significant impact of nutritional status on disease development (9). Scoring systems such as the Nutritional Risk Screening 2002 (NRS 2002) are recommended to identify patients at high nutritional risk, but this screening tool has not been validated for the specific population of patients with SAP.

The NRS 2002 was developed by Kondrup et al. two decades ago, and this nutritional risk assessment tool has since been used in patients with different diseases and been recommended by different guidelines (10–12). Nevertheless, there are no reports investigating and validating use of NRS 2002 in patients with SAP (8).

Heyland et al. previously proposed the Nutrition Risk in Critically Ill (NUTRIC) score, which is the first nutritional risk assessment tool developed and validated specifically for intensive care unit (ICU) patients and recommend by the American Society for Parenteral and Enteral Nutrition (ASPEN)/Society for Critical Care Medicine (SCCM) guidelines (12, 13). The score contains the variables of age, co-morbidities, days from hospital admission to ICU transfer, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and interleukin 6 (IL6). Applicability to routine clinical assessment was further expanded by waiving the requirement for determining IL6 in the modified NUTRIC score (mNUTRIC) (14). Many patients with SAP were admitted to the ICU because of systemic complications and failure of at least one organ. In that case, we considered whether both the NUTRIC and mNUTRIC scores, which were developed based on a population of critically ill patients, would be an option for a nutritional risk assessment tool for SAP patients. Unfortunately, neither the NUTRIC nor the mNUTRIC score have been validated in this population.

Thus, the purpose of this study was to investigate and potentially validate use of the NRS2002, NUTRIC score, and mNUTRIC score as nutritional risk assessment tools in SAP patients.

Materials and methods

Study design and patient enrollment

This was a retrospective study of patients suffering from SAP who were admitted to the ICU of Ruijin Hospital (China), a multidisciplinary unit in a university-affiliated tertiary care medical center, from January 2013 to December 2019. Adult patients (over 18 years of age) admitted to the ICU and diagnosed with SAP were included. SAP was diagnosed following the criteria of the Revised Atlanta Classification (1). The exclusion criteria were as follows: (1) ICU stay of less than 48 h; (2) abdominal surgery within 7 days before admission; (3) chronic pancreatitis; and (4) incomplete data. Given the nature of this retrospective observational study, no intervention, including nutritional practices, was made to standardize care. Enteral nutrition were managed to administered *via* nasojejunal tube within 72 h after admission. In cases of abdominal compartment syndrome and intolerance to enteral nutrition, supplement or total parenteral nutrition were started in not more than 10 days. The clinical protocols and management of patients was determined by the clinical team looking after the patient.

Outcome measures and data collection

The primary outcomes were defined as all-cause mortality at 28 and 90 days. Secondary outcomes were use of a mechanical ventilator, renal replacement therapy, and vasoactive agents during the hospital stay; continuous (>48) use of a mechanical ventilator, renal replacement therapy, and vasoactive agents during the hospital stay; proportion of multiple-organ dysfunction syndrome (MODS); proportion of surgical intervention; and ICU length of stay. MODS was defined as the combined dysfunction of two major organ systems (1, 15).

Time from ICU admission to the start of nutrition therapy was recorded. The nutrition strategy at day 7 was also collected. If the patients died within 7 days after admission, the latest nutrition strategy was collected. The average calorie and protein intakes were calculated. The total calorie requirements were calculated as 25–30 kcal/kg/day and 1.2–1.5 g/kg/day protein as in the current guidelines (12, 16). Ideal body weight was used for obese patients with BMI > 25 kg/m^2. The NRS 2002 was routinely performed and recorded at the time of ICU admission according to clinical practice. The CT severity index, Acute Physiology and Chronic Health Evaluation (APACHE II) scores, Sequential Organ Failure Assessment (SOFA) scores, NUTRIC scores, and mNUTRIC scores were calculated at the time of ICU admission. All clinical and laboratory parameters for the calculation of APACHE II, SOFA, NUTRIC, and mNUTRIC scores were recorded from the day of admission to ICU. Patients were followed up until death or observed for 90 days to conduct survival analyses 28 and 90 days after ICU admission.

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and expressed as the mean ± standard deviation (SD) for the normally distributed data and as the median and quartiles (25th–75th) for skewed data distributions. Two-tailed Student's *t*-test and Mann–Whitney test were used to analyze continuous data when appropriate. Categorical variables were presented as the number of cases. The Pearson chi-squared (χ^2) test and Fisher's exact test were used to analyze the categorical variables.

Receiver operating characteristic curves (ROC) were used to express the ability of different scoring systems for prediction of 28-day and 90-day mortalities *via* area under curve (AUC). Appropriate cut-offs were calculated by highest combined sensitivity and specificity using Youden's index. Patients were identified as being at high nutritional risk according to the calculated cut-off values. Survival analyses were performed according to the Kaplan–Meier curves; all deaths were recorded as events. The log-rank (Mantel–Cox) test was used for the comparison of survival curves. Relationship between 28-day mortality and nutrition strategy in patients identified as high nutritional risk by different tools was also analyzed. The effects of different screening tools on mortalities were also calculated using the Cox proportional hazards model. The results are reported as the hazard ratio (HR) with 95% confidence interval (CI). Subgroup analyses, with Cox proportional hazards adjusted for the same covariates as in the main model, were conducted to assess the interactions between different characteristics. The following prespecified baseline characteristics were analyzed: sex (male versus female); age (>55 versus ≤55); APACHE II score (≥8 versus <8); white-cell counts (>16,000 versus ≤16,000/mm^3); CT severity index (>6 versus ≤6); C-reactive protein level (>150 versus ≤150 mg/L); serum creatinine level (≥1.8 versus <1.8 mg/dl), and etiology (biliary versus non-biliary). Logistic regression was used to assess the strength of the association between the energy provision and 28-day mortality. Three logistic models including three different nutritional risk screening tools (the NRS 2002, NUTRIC score and mNUTRIC score), the energy provision and their product (interaction) were performed to assess if the nutritional risk screening tools modified the association between energy provision and 28-day mortality. Finally, the logistic models were run separately in patients categorized as low and high nutritional risk by three screening tools. The results are reported as the odds ratio (OR) with 95% CI. The statistical significance of lack of fit was tested by the Hosmere-Lemeshow goodness of fit test. The significance was assumed at a *p*-value <0.05. IBM SPSS Statistics software (version 25.0; Chicago, IL, United States) and GraphPad Prism 9.2 (GraphPad Software, La Jolla, CA, United States) were used for statistical analysis and plotting graphs.

Results

Patient characteristics

A total of 343 critically ill patients with SAP were initially included. Then, 49 patients were excluded for incomplete data, 26 were excluded for staying in the ICU less than 48 h, 24 were excluded for previous abdominal surgery, and 20 were excluded for chronic pancreatitis. A total of 234 patients were finally included in the analysis. The patient characteristics are presented in Table 1.

Clinical outcomes predicted by the NRS 2002, NUTRIC, and mNUTRIC

The 28-day mortality was 7.7%, and the 90-day mortality was 12.8%. The mortality rates in SAP patients according to the NRS 2002, NUTRIC, and mNUTRIC are illustrated in Supplementary Figure S1. The predictive ability for 28-and 90-day mortality risk were analyzed by ROC, and the results are shown in Figures 1, 2. As depicted in Figures 1, 2, both the NUTRIC and mNUTRIC showed a reasonable ability to predict 28-and 90-day mortality in SAP patients. The NUTRIC and mNUTRIC performed better than the NRS 2002 in predicting both the primary and secondary outcomes.

The NUTRIC (AUC = 0.861, 95% CI: 0.794–0.929, $p < 0.001$) and mNUTRIC (AUC = 0.838, 95% CI: 0.768–0.908, $p < 0.001$) showed a higher predictive value than the NRS 2002 (AUC = 0.706, 95% CI: 0.595–0.817, $p = 0.004$), and thus better performance, in predicting 28-day mortality. In the prediction of 28-day mortality, the highest combined sensitivity and specificity of the NRS 2002 was found with a cut-off value of ≥5 (sensitivity = 88.9%, specificity = 52.1%). The NUTRIC had a cut-off value of ≥3 (sensitivity = 100%, specificity = 43.1%). The cut-off value of the mNUTRIC was also found at ≥3 (sensitivity = 100%, specificity = 42.6%). The NUTRIC (AUC = 0.871, 95% CI: 0.818–0.925, $p < 0.001$) and mNUTRIC (AUC = 0.828, 95% CI: 0.754–0.891, $p < 0.001$) also performed better than the NRS 2002 (AUC = 0.695, 95% CI: 0.604–0.787, $p = 0.001$) in predicting 90-day mortality. The cut-off values were the same in predicting the 28-day and 90-day mortality (≥5 for NRS 2002 and ≥3 for both NUTRIC and mNUTRIC). The results of the ROC analyses to predict the clinical outcomes are shown in Table 2.

The NUTRIC and mNUTRIC had similar performance in predicting secondary outcomes. The NRS 2002 was the least valuable scoring system for predicting the clinical outcomes. All three scoring systems had no prognostic relevance with the use or continuous use (>48 h) of renal replacement therapy in patients with SAP. A comparison of the clinical outcomes in SAP patients categorized as high nutritional risk and low nutritional risk is shown in Table 3. Other characteristics are demonstrated in Supplementary Table S1.

TABLE 1 Patient characteristics.

Variables	Overall population (n=234)
Demographics	
Age (years)	47 (37–62)
Sex (male, %)	156 (66.7)
BMI (kg/m^2)	23.7 ± 3.9
NRS 2002	5 (4–5)
NUTRIC	3 (2–4)
mNUTRIC	3 (2–4)
APACHE II	9 (5–13)
SOFA	4 (2–6)
CT severity index at admission	6 (4–7)
MAP at admission (mmHg)	100 (92–111)
Calories received within first week (kcal/kg/day)	15.4 ± 3.2
Etiology	
Biliary (n, %)	91 (38.9)
Alcoholic (n, %)	62 (26.5)
Hypertriglyceridemia (n, %)	62 (26.5)
Other (n, %)	19 (8.1)
Laboratory test	
PCT at admission (ng/ml)	1.1 (0.4–6.1)
CRP at admission (mg/L)	180 (91–249)
White-cell count at admission (/mm^3)	13,020 (9590–17,320)
Serum creatinine at admission (mg/dl)	0.8 (0.6–1.3)
Serum amylase at admission (IU/L)	511 (197–1,163)
Clinical outcomes	
28-day mortality (n, %)	18 (7.7)
90-day mortality (n, %)	30 (12.8)
Length of ICU stay (days)	30 (18–44)
Surgical intervention (n, %)	25 (10.7)
Use of mechanical ventilator (n, %)	194 (82.9)
Renal replacement therapy (n, %)	83 (35.5)
Use of vasoactive agent (n, %)	36 (15.4)
Use of mechanical ventilator >48 h (n, %)	31 (13.3)
Renal replacement therapy >48 h (n, %)	55 (23.5)
Use of vasoactive agent >48 h (n, %)	22 (9.4)
MODS (n, %)	75 (32.1)

BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; NUTRIC, Nutrition Risk in Critically Ill; mNUTRIC, modified Nutrition Risk in Critically Ill; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; CRP, C-reactive protein; MAP, mean artery pressure; MODS, multiple-organ dysfunction syndrome.

Energy intake and mortality risk analyses

Survival analyses by Kaplan–Meier (Figures 3–5) showed significant differences depending on different scoring levels. By day 28, a total of 18 (7.6%) patients had died. Of these, 16 patients were categorized as high nutritional risk according to the NRS 2002, while all 18 patients were identified as high nutritional risk according to the NUTRIC and mNUTRIC scores and the cut-off values calculated in the previous part of this study. The Cox proportional hazards regression analysis of factors associated with mortality are shown in Table 4. The SAP patients with higher NRS 2002 (HR = 2.889, 95% CI: 1.278–6.528, p = 0.011), NUTRIC (HR = 1.691, 95% CI: 1.331–2.148, p < 0.001), and mNUTRIC (HR = 1.689, 95% CI: 1.292–2.207, p < 0.001) scores had a higher risk of short-term mortality.

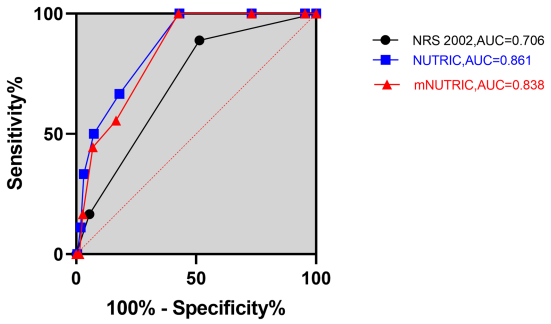

FIGURE 1
Prognostic accuracy of the NRS 2002, NUTRIC, and mNUTRIC to predict 28-day mortality analyzed by receiver operating characteristic curves. The black line with cycle represents the results of the NRS 2002 (AUC=0.706, 95% CI: 0.595–0.817, p=0.004). The blue line with square represents the results of the NUTRIC (AUC=0.861, 95% CI: 0.794–0.929, p<0.001). The red line with triangle represents the results of the mNUTRIC (AUC=0.838, 95% CI: 0.768–0.908, p<0.001).

Similar results were also revealed in the long-term mortality. In total, 30 (12.8%) patients had died by day 90. The NRS 2002 (HR = 2.461, 95% CI: 1.286–4.713, p = 0.007) failed to identify 4 of these, and the mNUTRIC (HR = 1.683, 95% CI: 1.359–2.083, p < 0.001) failed to identify 1 of these, whereas the NUTRIC (HR = 1.747, 95% CI: 1.441–2.118, p < 0.001) correctly categorized all patients. The results of the subgroup analyses are reported in Supplementary Figure S3 (28-day mortality) and Supplementary Figure S4 (90-day mortality). The effects of the NRS 2002, NUTRIC, and mNUTRIC were consistent across all subgroups.

All patients started enteral nutrition by nasogastric or nasojejunal feeding within 72 h after admission. During the first week after admission to ICU, the calories received were 15.4 ± 3.2 kcal/kg/day, on average. The average protein intake was 0.7 ± 0.2 g/day. If the target of calorie target is set as 25–30 kcal/kg/day, in accordance with current guidelines, only 130 (56%) patients received more than 60% of caloric adequacy. The median energy provision was 61.5 with an interquartile range from 53.1 to 68.8. Energy provision was not correlated with the NRS 2002, NUTRIC score or mNUTRIC score. Mortality generally decreased with increasing energy provision, and the Hosmere-Lemeshow goodness of fit test showed that the calibration of the model was statistically ideal (p = 0.386). Using these validation data, the logistic model estimated odds of mortality were multiplied by 0.822 (95% CI, 0.682–0.956, p = 0.015) for every 1 kcal/kg/day increase on the energy provision. Separate models confirmed the results in high nutritional risk group (high NRS 2002 group, OR = 0.808, 95% CI: 0.701–0.963, p = 0.013; high NUTRIC score group, OR = 0.826, 95% CI: 0.702–0.972, p = 0.021; and high mNUTRIC score group, OR = 827, 95% CI: 0.703–0.973, p = 0.022) while patients categorized as low

nutritional risk did not show the benefits of higher energy provision rate (low NRS 2002 group: OR = 1.172, 95% CI: 0.712–1.928, $p = 0.533$; Models were not applicable for no patients died in low NUTRIC or low mNUTRIC group within 28 days). The test for interaction confirmed the association between energy provision and mortality is significantly modified by the NUTRIC score (test for interaction $p < 0.001$) and the mNUTRIC score (test for interaction $p < 0.001$) while the interaction was not modified by the NRS 2002(test for interaction $p = 0.166$). Figures 6–8 demonstrate that increased calorie intake during the first week is associated with increased short-term survival in patients categorized as high nutritional risk by the NUTRIC, or mNUTRIC. No statistical difference was found in the calories received during the first week after admission in different nutritional risk groups. The detailed results were shown in Supplementary Table S1.

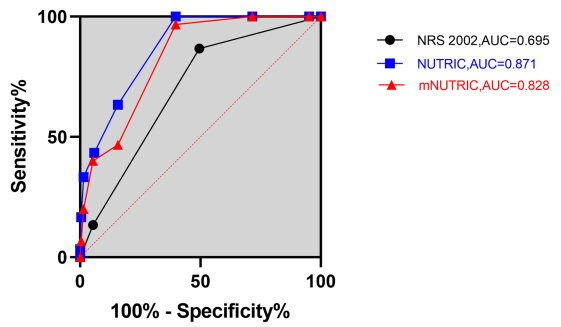

FIGURE 2
Prognostic accuracy of the NRS 2002, NUTRIC, and mNUTRIC to predict 90-day mortality analyzed by receiver operating characteristic curves. The black line with cycle represents the results of the NRS 2002 (AUC=0.695, 95% CI: 0.604–0.787, p=0.001). The blue line with square represents the results of the NUTRIC (AUC=0.871, 95% CI: 0.818–0.925, p<0.001). The red line with triangle represents the results of the mNUTRIC (AUC=0.828, 95% CI: 0.754–0.891, p<0.001).

Discussion

Unfortunately, no treatments were proven effective to suppress the powerful cascade of inflammatory factors associated with SAP (17). With this limitation, the current treatment method of SAP is primarily supportive and nutrition support is considered a major method in treating SAP patients. Nutritional risk assessment of SAP patients is an important element for outcome prediction. Many possible features can lead to malnutrition in SAP patients. Many possible features can lead to malnutrition in this population. In this study, considering that two peaks (short-term and long-term) of mortality are observed for SAP patients, we chose to investigate the prognostic accuracy of the NRS 2002, NUTRIC, and mNUTRIC in predicting the 28- and 90-day mortality of SAP patients (18–21). The NUTRIC demonstrated the highest prediction value among the three scoring systems. A similar prognostic accuracy was found for the mNUTRIC. In the absence of IL-6, the mNUTRIC can equally predict the clinical outcomes of SAP patients.

In SAP patients, early death usually occurs as a result of systemic inflammatory response syndrome (SIRS) and MODS (22). SIRS is often caused by the release of various cytokines in the first 2 weeks. Shinzeki et al. (20) reported that early death accounted for 22% (5/23) of all deaths in their study, and we observed a similar figure in our study, wherein 7 (23%) patients died during the first 2 weeks (Supplementary Figure S3) and were well identified by the NUTRIC and mNUTRIC. Acute underfeeding is a possible consequence, and it can lead to immunosuppression and to inflammatory response impairment, which may occur in SAP patients and cause early death. Furthermore, in clinical practice, determining an appropriate target for nutrient supplementation of patients at high risk of malnutrition is crucial. Similar with the previous study, identifying patients with high mNTURIC scores and supporting them with adequate nutrition during an ICU stay would be useful in improving clinical outcomes such as 90-day mortality (23). Due to the nature of the retrospective

TABLE 2 Prognostic accuracy of the NRS2002, NUTRIC, and mNUTRIC to predict clinical outcomes analyzed by ROC.

Clinical outcomes	NRS 2002			NUTRIC			mNUTRIC		
	AUC	95% CI	*p*-Value	AUC	95% CI	*p*-Value	AUC	95% CI	*p*-Value
28-day mortality	0.706	0.594–0.817	0.004	0.861	0.794–0.929	<0.001	0.838	0.768–0.908	<0.001
90-day mortality	0.695	0.604–0.787	0.001	0.871	0.818–0.925	<0.001	0.828	0.764–0.891	<0.001
Surgical intervention	0.661	0.561–0.761	0.009	0.727	0.637–0.817	<0.001	0.696	0.605–0.787	0.001
Use of mechanical ventilator	0.658	0.571–0.745	0.002	0.716	0.618–0.815	<0.001	0.717	0.619–0.815	<0.001
Renal replacement therapy	0.575	0.500–0.650	0.057	0.545	0.458–0.632	0.257	0.537	0.451–0.624	0.348
Use of vasoactive agent	0.678	0.585–0.771	0.001	0.730	0.622–0.839	<0.001	0.712	0.604–0.819	<0.001
Use of mechanical ventilator >48 h	0.663	0.565–0.760	0.004	0.698	0.609–0.787	<0.001	0.686	0.599–0.774	0.001
Renal replacement therapy >48 h	0.547	0.463–0.632	0.288	0.550	0.444–0.656	0.262	0.542	0.437–0.646	0.349
Use of vasoactive agent >48 h	0.664	0.552–0.776	0.011	0.709	0.584–0.834	0.001	0.683	0.559–0.806	0.005
MODS	0.702	0.633–0.771	<0.001	0.754	0.686–0.823	<0.001	0.741	0.672–0.810	<0.001

TABLE 3 Comparison of clinical outcomes in SAP patients categorized as high nutritional risk and low risk by the NRS2002, NUTRIC, and mNUTRIC.

Clinical outcomes	NRS 2002			NUTRIC			mNUTRIC		
	0–4 (*n*=107)	5–6 (*n*=127)	*p*-Value	0–2 (*n*=123)	3–8 (*n*=111)	*p*-Value	0–2 (*n*=124)	3–7 (*n*=110)	*p*-value
28-day mortality (*n*, %)	2 (1.9)	16 (12.6)	0.002	0 (0.0)	18 (16.2)	<0.001	0 (0.0)	18 (16.4)	<0.001
90-day mortality (*n*, %)	4 (3.7)	26 (20.5)	<0.001	0 (0.0)	30 (27.0)	<0.001	1 (0.8)	29 (26.4)	<0.001
ICU length of stay (days)	29 (18–39)	30 (18–47)	0.184	31 (18–40)	29 (18–48)	0.582	31 (18–40)	29 (18–48)	0.681
Surgical intervention (*n*, %)	4 (3.7)	21 (16.5)	0.001	4 (3.3)	21 (18.9)	<0.001	5 (4.0)	20 (18.2)	<0.001
Use of mechanical ventilator (*n*, %)	79 (73.8)	115 (90.6)	<0.001	94 (76.4)	100 (90.1)	<0.001	95 (76.6)	99 (90.0)	<0.001
Renal replacement therapy (*n*, %)	28 (26.2)	55 (43.3)	<0.001	39 (31.7)	44 (39.6)	<0.001	39 (31.5)	44 (40.0)	<0.001
Use of vasoactive agent (*n*, %)	7 (6.5)	29 (22.8)	0.001	10 (8.1)	26 (23.4)	0.001	10 (8.1)	26 (23.6)	0.001
Use of mechanical ventilator >48 h (*n*, %)	6 (5.6)	25 (19.7)	0.002	9 (7.3)	22 (19.8)	0.005	9 (7.3)	22 (20.0)	0.004
Renal replacement therapy >48 h (*n*, %)	20 (18.7)	35 (27.6)	0.111	24 (19.5)	31 (27.9)	0.130	24 (19.4)	31 (28.2)	0.112
Use of vasoactive agent >48 h (*n*, %)	4 (3.7)	18 (14.2)	0.006	5 (4.1)	17 (15.3)	0.003	5 (4.0)	17 (15.5)	0.003
MODS (*n*, %)	13 (12.2)	62 (48.8)	<0.001	20 (16.3)	55 (49.6)	<0.001	21 (16.9)	54 (49.1)	<0.001

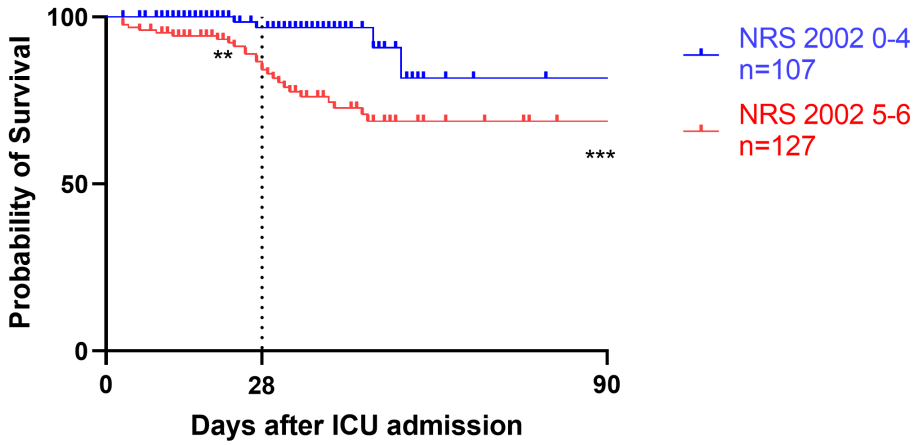

FIGURE 3
Kaplan–Meier survival analyses depending on baseline scores of low NRS 2002 0-4 (blue line, *n*=107) versus high NRS 2002 5-6 (red line, *n*=127); **$p<0.05$, ***$p<0.001$.

study, nutrition therapy after day 7 was not included into the analysis, due to the high heterogeneity in the nutrition intake methods. Some patients started oral food intake, and thus, the calorie intake after day 7 was not counted. Hence, we only investigated the effect of nutrition therapy during the first week after admission. In our study, the relationship between nutrition therapy in the first week and short-term mortality was revealed, showing a lower mortality with a higher calorie intake in patients at high nutritional risk. On the other hand, severe disease can also cause acute gastrointestinal injury and a decrease in calorie intake. The organs that most commonly fail in acute pancreatitis include those linked with respiratory, renal, and circulatory failure, while few

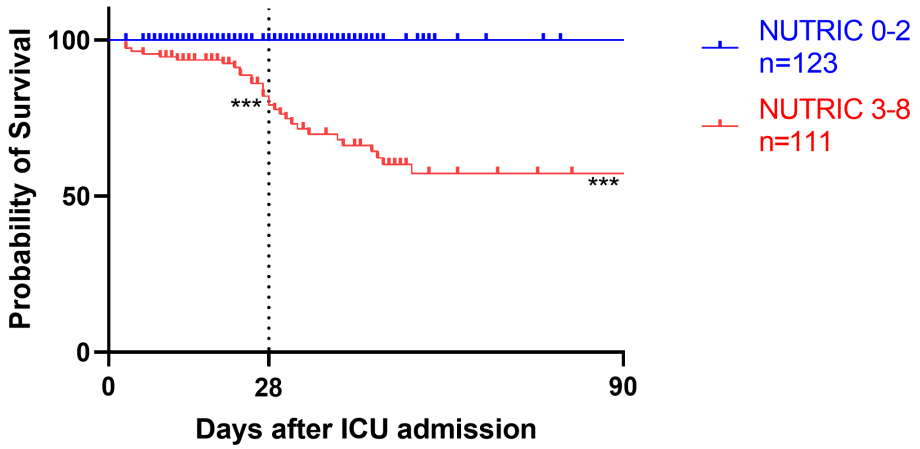

FIGURE 4
Kaplan–Meier survival analyses depending on baseline scores of low NUTRIC 0-2 (blue line, *n*=123) versus high NUTRIC 3-8 (red line, *n*=111); ***$p<0.001$.

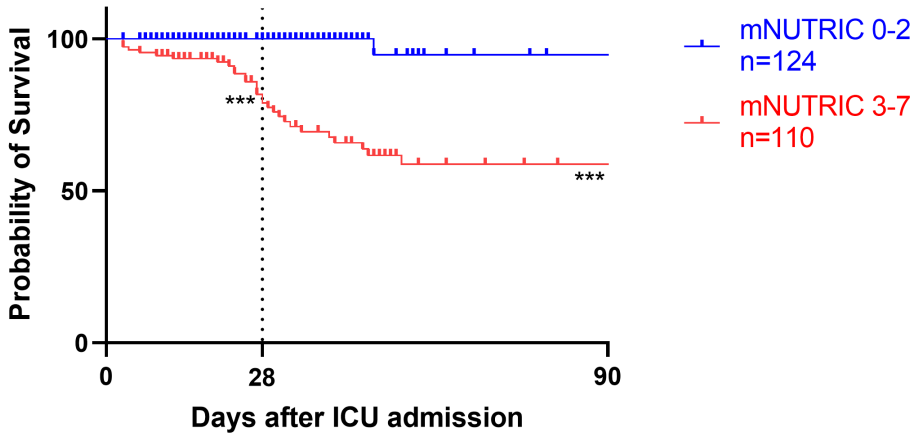

FIGURE 5
Kaplan–Meier survival analyses depending on baseline scores of low mNUTRIC 0-2 (blue line, *n*=124) versus high mNUTRIC 3-7 (red line, *n*=110); ***$p<0.001$.

studies have focused on gastrointestinal failure. Studies have shown that gastrointestinal dysfunction and failure could be an important determinant of outcome in critically ill patients, including acute pancreatitis. Sun et al. (24) suggested that gastrointestinal failure is an accurate predictor of SAP prognosis. Other studies have revealed that gastrointestinal symptoms are frequent in patients in the ICU (25, 26). A total of 62% of patients exhibited at least one gastrointestinal symptom for at least 1 day (27). There is also increasing evidence that the development of gastrointestinal problems is related to a poor outcome in critically ill patients (28). The NUTRIC and mNUTRIC do not include gastrointestinal symptoms, which could thus be a source of bias for a specific group of patients. Regardless, acute underfeeding should be considered as a major complication in SAP.

In the analyses of long-term mortality, the NUTRIC and mNUTRIC also showed better prognostic value than the NRS 2002. As a result, we determined different cut-off values for the NUTRIC and mNUTRIC than a previous study in identifying critically ill SAP patients at a high nutritional risk. According to Youden's index, we found a cut-off value of ≥3 for both NUTRIC and mNUTRIC to be more appropriate for predicting short-term and long-term mortality. Heyland et al. and Rahman et al. utilized ≥5 (mNUTRIC) and ≥6 (NUTRIC) as cut-off values in critically ill patients when the NUTRIC and mNUTRIC were first introduced (13, 14). De Vries et al. (29) found the best discriminative ability with a mNUTRIC cut-off >4 for 28-day mortality in mechanically ventilated patients. Mayr et al. (30) determined a cut-off value of ≥6 to predict 90-day mortality and a cut-off value of ≥7 to predict 28-day mortality in cirrhotic patients (for both NUTRIC and mNUTRIC). In contrast, Jeong et al. (31) found a cut-off value ≥6 for the mNUTRIC in predicting 28-day mortality. Different cut-off values have thus been found when investigating patients suffering from different diseases. A lower cut-off value of the NUTRIC and mNUTRIC in SAP patients was found in our study in comparison to other studies focusing on different populations. This difference could result from the catabolic nature of SAP and differences in the characteristics of specific diseases. The

TABLE 4 Cox proportional hazards regression model for mortalities.

Screening tools	Unadjusted			Adjusted*		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
28-day mortality						
NRS 2002	3.026	1.469–6.234	0.003	2.889	1.278–6.528	0.011
NUTRIC	1.799	1.436–2.254	<0.001	1.691	1.331–2.148	<0.001
mNUTRIC	1.792	1.393–2.305	<0.001	1.689	1.292–2.207	<0.001
90-day mortality						
NRS 2002	2.605	1.464–4.635	0.001	2.461	1.286–4.713	0.007
NUTRIC	1.852	1.541–2.224	<0.001	1.747	1.441–2.118	<0.001
mNUTRIC	1.788	1.460–2.190	<0.001	1.683	1.359–2.083	<0.001

*Hazard ratio (95% CI) and *p*-value calculated with Cox proportional hazards model with adjustment for baseline value of PCT.

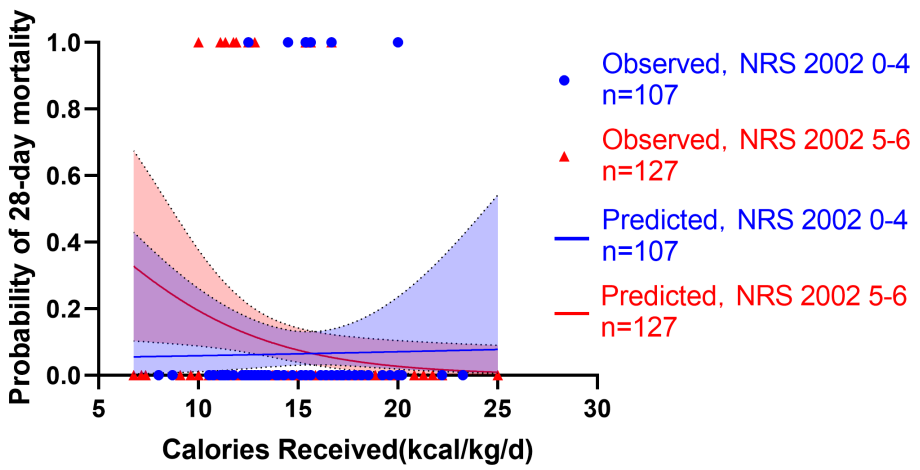

FIGURE 6
Predicted probability of 28-day mortality versus calories received by low NRS 2002 0-4 (blue line, *n*=107) versus high NRS 2002 5-6 (red line, *n*=127). Blue cycles represent the low NRS 2002 cases while red triangles represent the high NRS 2002 cases. Test for interactions were assessed by a logistic model including the NRS 2002, the energy provision and their product (interaction). The NRS 2002 was found unable to modify the relationship between energy provision during first week and 28-day mortality (*p*=0.166).

classic cut-off values cannot well identify SAP patients at nutritional risk, especially using the NRS 2002. All patients from our study were classified as at nutritional risk by utilizing the classic NRS 2002 cut-off value ≥3.

The severity of acute pancreatitis is defined by the presence or absence of organ failure, local complications, or both (1). Local complications or the occurrence of single-organ failure in SAP patients may only result in mild systemic symptoms at the early stage of AP, which could lead to a lower score of SOFA and APACHE II at admission. Lower Glasgow coma scores were observed in SAP patients compared with other critically ill patients upon admission to the ICU. A severe complication of SAP is acute gastrointestinal injury, which cannot be well stratified by the NUTRIC and mNUTRIC. Acute gastrointestinal injury is often underestimated while it could be lethal in SAP patients. All these reasons could result in a lower cut-off value of the NUTRIC and mNUTRIC in SAP patients. Also, APACHE II score <8 at admission may be a predictive factor for the risk of death in 90 days among patients categorized as high nutritional risk by NUTRIC and mNUTRIC (interaction $p < 0.05$). Patients at nutritional risk with lower APACHE II score appeared to have more co-morbidity and delayed longer before admission to ICU than those without. The results for analysis of secondary outcomes were similar to those of the primary outcomes. Only the prediction ability of MODS was rather accurate, with an AUC ≥ 0.75, although the NUTRIC score still showed a better prediction ability for most secondary outcomes. Explanation for the shortcomings of the NUTRIC score is that mortality was the only consideration in the study design when it was first developed (13). Some experts claim that mortality is not the only outcome that should be assessed when determining the efficacy of a nutritional intervention, considering the numerous factors influencing ICU mortality (16). Long-term functional tests might better reflect the benefit of a nutritional intervention and should be included in the screening tools (32). The present results of our study underline the need for further studies utilizing individualized nutritional risk assessment tools based on the NRS 2002, NUTRIC, mNUTRIC or other scoring systems.

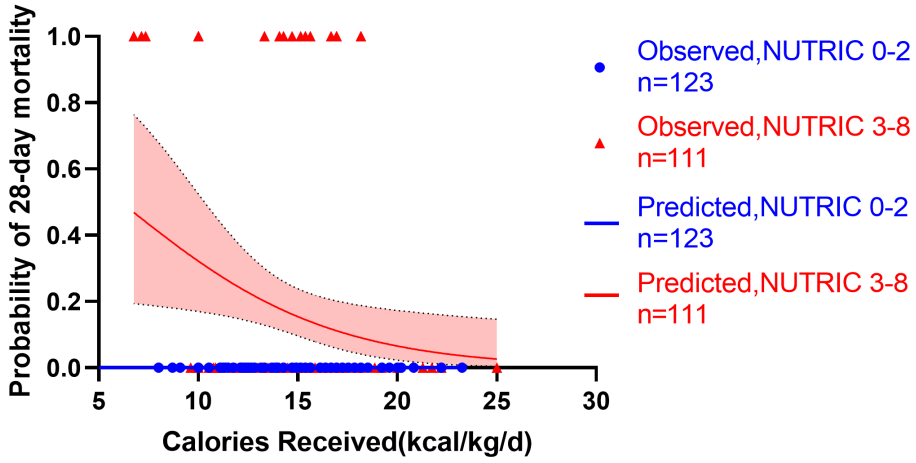

FIGURE 7
Predicted probability of 28-day mortality versus calories received by low NUTRIC 0-2 (blue line, *n*=123) versus high NUTRIC 3-8 (red line, *n*=111). Blue cycles represent the low NUTRIC score cases while red triangles represent the high NUTRIC score cases. Test for interactions were assessed by a logistic model including the NUTRIC score, the energy provision and their product (interaction). The test for interaction confirmed the association between energy provision and mortality is significantly modified by the NUTRIC score (test for interaction $p<0.001$).

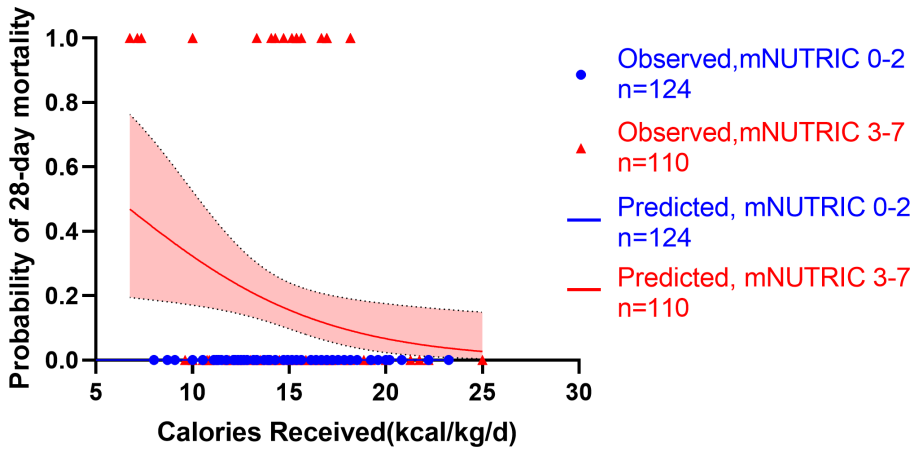

FIGURE 8
Predicted probability of 28-day mortality versus calories received by low mNUTRIC 0-2 (blue line, *n*=124) versus high mNUTRIC 3-7 (red line, *n*=110). Blue cycles represent the low NUTRIC score cases while red triangles represent the high NUTRIC score cases. Test for interactions were assessed by a logistic model including the NUTRIC score, the energy provision and their product (interaction). The test for interaction confirmed the association between energy provision and mortality is significantly modified by the mNUTRIC score (test for interaction $p<0.001$).

Although this study included a reasonable number of patients with SAP, and the results of this study were conclusive with statistical significance, this study has several limitations. The first is that it is a retrospective single-center study. The 28- and 90-day mortalities are defined as the primary outcomes, as there is no gold standard to judge the fitness and accuracy of a nutritional risk screening tool. The study focuses on the assessment of the NRS2002, NUTRIC, and mNUTRIC scores, which were obtained at the time of admission to ICU, whereas no further evaluation was conducted during the course of the disease in the ICU. Although the NUTRIC and mNUTRIC show good prognostic value for 90-day mortality, many other factors should be taken into consideration. Moreover, no interventions occurred during the study. Nutrition therapy after day 7 was not included in the analyses due to the heterogeneity in nutrition intake methods thereafter. The effects of the nutritional therapy on the outcomes of patients with high nutritional risk were thus not fully assessed. Further prospective interventional studies focusing on nutrition therapy based on the NRS2002, NUTRIC, or mNUTRIC are needed to support the findings.

Conclusion

In conclusion, the NUTRIC and mNUTRIC demonstrated a prognostic advantage comparison with the NRS 2002 in predicting SAP patients at high nutritional risk. Moreover, both NUTRIC and mNUTRIC scores can adequately identify SAP patients at high nutritional risk.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ruijin Hospital Ethics Committee, Shanghai Jiaotong University School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

DC and BZ drafted and wrote the manuscript. DC, BZ, LW, and YQ collected the data. WG, XB, EC, and FJ analyzed the data. DC, BZ, and JH designed the study. EM, HS, and JH revised the manuscript and supervised the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1101555/full#supplementary-material

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Temporal and periorbital depressions identified by 3D images are correlated with malnutrition phenotypes in cancer patients: A pilot study

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Background: Prompt diagnosis of malnutrition and appropriate interventions can substantially improve the prognosis of patients with cancer; however, it is difficult to unify the tools for screening malnutrition risk. 3D imaging technology has been emerging as an approach to assisting in the diagnosis of diseases, and we designed this study to explore its application value in identifying the malnutrition phenotype and evaluating nutrition status.

Methods: Hospitalized patients treating with maintenance chemotherapy for advanced malignant tumor of digestive system were recruited from the Department of Oncology, whose NRS 2002 score>3. Physical examination and body composition data of patients at risk for malnutrition were analyzed by physicians trained to complete a subjective global assessment. The facial depression index was recognized using the Antera 3D® system, temporal and periorbital depression indexes were acquired using the companion software Antera Pro. This software captures quantitative data of depression volume, affected area, and maximum depth of temporal and periorbital concave areas.

Results: A total of 53 inpatients with malnutrition-related indicators were included. The volume of temporal depression was significantly negatively correlated with upper arm circumference (r=−0.293, p=0.033) and calf circumference (r=−0.285, p=0.038). The volume and affected area of periorbital depression were significantly negatively correlated with fat mass index (r=−0.273, p=0.048 and r=−0.304, p=0.026, respectively) and percent body fat (r=−0.317, p=0.021 and r=−0.364, p=0.007, respectively). The volume and affected area of temporal depression in patients with muscle loss phenotype (low arm circumference/low calf circumference/low handgrip strength/low fat-free mass index) were significantly higher than those in patients without muscle loss. Moreover, patients with fat mass loss phenotype (low fat mass index) showed a significant increase in the volume and affected area of periorbital depression.

Conclusion: The facial temporal region, and periorbital depression indicators extracted by 3D image recognition technology were significantly associated with the phenotype of malnutrition-related muscle and fat loss and showed a trend of grade changes in the population of different subjective global assessment nutritional classifications.

KEYWORDS
cancer, three-dimensional images, temporal muscle, phenotype, malnutrition

1. Introduction

Patients with cancer usually have the highest incidence of malnutrition among hospitalized patients as both the disease and treatment can lead to alterations in energy expenditure and energy intake (1). Malnutrition reduces sensitivity to drugs, decreases quality of life, and directly increases the risk of all-cause mortality (2). Prompt diagnosis of malnutrition and appropriate interventions can significantly improve the prognosis of patients with cancer (3). Therefore, screening for malnutrition risk at admission is recommended for all patients with cancer; however, screening tools differ between regions and organizations.

In the past few decades, screening for malnutrition including a comprehensive assessment of the patients' weight changes, food intake, and functional levels has mainly been performed through subjective assessments by clinicians and nutritionists (4). Due to the differences in target populations and evaluation methods, it is challenging to standardize the evaluation of the malnutrition status of patients. In recent years, associations such as the European Society for Clinical Nutrition and Metabolism and American Society for Parenteral and Enteral Nutrition (ASPEN) have reached agreement on the application of dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), and other objective assessment indicators for quantifying the muscle and fat mass for diagnosis of malnutrition (5). Through extensive clinical applications, cut-off values of these indicators have been established in various populations. The clinical value of muscle mass and fat mass assessments in the diagnosis of malnutrition has gradually received increasing attention.

The psoas index, quantified by CT imaging of the third lumbar spine (L3), has been recognized as an important indicator of muscle loss, and is significantly associated with morbidity and long-term prognosis in patients with cancer (6). A comprehensive assessment of the changes in body composition at different anatomical locations (carina, thoracic, and lumbar spine) using multiple levels of CT imaging has also been found to be useful in predicting the prognosis of lung transplant patients (7). However, because DXA, CT, and MRI are not widely used in the assessment of malnutrition in clinical practice, and due to their relatively high cost, some simple and available surrogate indicators are used to evaluate muscle loss, such as the circumference of the upper arm and calf and bioelectrical impedance analysis (BIA) of body composition (8).

In a recent study, temporal muscle thickness (TMT) assessed using 3D imaging technology was used as a quantitative muscle biomarker for predicting progression-free survival and overall survival in patients with primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) (9). This study demonstrated the utility of computer-assisted image recognition techniques for accurate measurement of body composition. 3D image recognition is an advanced technology that uses computer programs to assist with identification of image features. This technology can discern subtle changes that are difficult to detect by visual examination alone, and can integrate the characteristics of many variables for computational analysis. It has been widely used in recent years to assist in clinical diagnosis.

3D facial image recognition has demonstrated its clinical application in the analysis of typical facial features of acromegaly (10), differential diagnosis of various genetic syndromes involving facial deformities (11), and diagnosis and analysis of treatment efficacy of skin lesions (12). Moreover, the simplicity of capturing 3D facial images using mobile phone applications makes this auxiliary diagnosis method more accessible, and therefore more conducive in various clinical and preclinical settings.

To explore the application value of 3D facial image recognition technology in assisting the diagnosis of malnutrition, we piloted a 3D facial image recognition method for hospitalized patients with cancer. We aimed to verify its applicability in determining the phenotype related to malnutrition, using measures such as the reduction in muscle and fat mass, and thus provided a methodological reference for simplifying the clinical diagnosis of malnutrition.

2. Methods

2.1. Study population

Hospitalized patients treating with maintenance chemotherapy for advanced malignant tumor of digestive system were recruited from the Department of Oncology, Peking Union Medical College Hospital. The inclusion criteria were: (1) Han race, (2) age > 18 years, (3) nutritional risk screening (NRS 2002) score > 3, and (4) voluntary participation and cooperation for facial image collection. The exclusion criteria were: (1) artificial changes in the face (for example, facial plastic surgery or trauma, head and neck radiotherapy); (2) special diseases with facial changes (for example, acromegaly, hyperthyroidism); (3) administration of high-dose glucocorticoids leading to facial changes; (4) edema of the face or limbs; and (5) other situations deemed for exclusion by the researchers. This study was approved by the Ethics Committee of the Peking Union Medical College Hospital (Number: JS-2768), and all participants provided written informed consent.

2.2. Malnutrition phenotypic assessment

Prior to the start of the trial, two physicians were uniformly trained in the content and standard procedures of nutritional assessments, and any doubts and inconsistencies were discussed and resolved. Physicians were trained to complete NRS 2002 and subjective global assessment (SGA) nutritional assessment by applying structured questionnaires within 24 h of patient admission and conducting a standardized physical examination, which included measurement of height, weight, upper arm circumference, calf

circumference, handgrip strength (HGS), and body composition analysis.

NRS 2002 and SGAs were performed in accordance with the guidelines of the American Society for Parenteral and Enteral Nutrition and were derived from the patient's medical history and physical examination. The medical history included weight, appetite changes, gastrointestinal symptoms, mobility, and disease-related nutritional requirements over the past 2 weeks. Physical examination included subcutaneous fat (triceps and chest), muscle mass (including the quadriceps and deltoid), and edema levels. Based on the above assessments, patients were classified into grades A, B, and C, with grades B and C considered to have mild-to-moderate and severe malnutrition, respectively.

Weight (kg) and height (cm) were measured in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2). The upper arm circumference (AC) and calf circumference (CC) were measured using a non-elastic tape, with a minimum reading of 0.1 cm. With the patient in a sitting position, the circumference of the relaxed non-dominant arm at the midpoint of the line connecting the acromion and olecranon was measured. Additionally, with the patient sitting on the side of the bed, the relaxed calf was measured on a plane perpendicular to the long axis of the calf to obtain the maximum circumferential value. HGS was measured using an electronic handgrip dynamometer with the patient standing comfortably, repeated three times with the lateral hand; the maximum value was used for the analysis.

Body composition analysis of the patients was performed using BIA in a supine position with arms held away from the body and legs apart. When the patients were unable to take the supine position, the sitting position was used for BIA measurement (only two of all the subjects). Fat-free mass (FFM), fat mass (FAT), visceral fat mass (VFA), and percent body fat (PBF) were measured using a portable body composition meter (InBody S10); the fat-free mass index (FFMI) and fat mass index (FMI) were calculated as FFM and FAT (kg) divided by height (m), respectively.

2.3. 3D facial image recognition

Facial depression index recognition was performed using the Antera 3D® system within 24 h of patient admission, using a camera for acquisition and analysis of skin images, with an area of 56 mm × 56 mm. The camera utilizes light-emitting diodes (LEDs) of different wavelengths to illuminate the skin from different directions and then performs computer-assisted 3D skin surface reconstruction based on spatial and spectral analysis of the acquired image data (13). The reconstructed skin texture using the shape from shading technique was used for quantitative skin analysis, and different filters (14) were available for the measurement of specific skin features such as wrinkles, texture, pores, depressions, and elevations. Volume-related measurements were generated by interpolating the information from the boundaries of the selected region to determine the enclosed volume. The camera opening was placed directly on the skin, and the image was unaffected by external lighting conditions. This was achieved through a combination of polarizing filters and proprietary technology, ensuring that the results were accurate and reproducible (15).

Depression index of temporal (between the outer edge of the orbit and the hairline) and periorbital (the upper edge was the brow arch, covering the entire orbit) were acquired using the camera companion software Antera Pro (v2.8.2; Miravex Limited, Dublin, Ireland) (16). This software analyzed the skin texture of the pre-specified target area (area indicated by the circle in Figure 1), and obtained the quantitative data of depression volume, affected area, and maximum depth of temporal (TEM) (diameter = 30.8 mm) and periorbital (ORB) (diameter = 54.1 mm) concave areas (purple, blue, and green regions in Figure 1; gray region represents the reference level).

2.4. Malnutrition phenotype groups

To compare differences in depression indicators among different groups of malnutrition phenotype, the phenotypes were grouped according to the results of previous studies and guidelines. Among the phenotypes associated with decreased muscle mass, upper arm circumference (AC) cutoffs were <27 cm in men and <25 cm in women (17). and calf circumference (CC) cutoff was <33 cm in men and <32 cm in women (18). According to the 2019 Consensus Update on Sarcopenia Diagnosis and Treatment developed by the Asian Working Group for Sarcopenia, the criteria for low HGS are <28 kg in men and <18 kg in women (19); and the cut-off FFMI calculated from body composition measurements is <17 kg/m^2 in men and <15 kg/m^2 in women. Malnutrition phenotypes associated with reduced fat mass were FMI with cut-off value of <7.7 kg/m^2 in men and <5 kg/m^2 in women (20).

2.5. Statistical analysis

Previous studies have shown that the incidence of malnutrition in hospitalized patients with cancer in China was approximately 38.9% (21); the type I error α was relaxed to 0.25 in a pilot study (22), and the permissible error δ was set at 0.078. Thus, at least 52 patients had to be included in this study. All statistical analysis was performed using the SPSS statistical software version 22.0 (IBM Corp., Armonk, NY, United States). Continuous variables were expressed as the mean ± standard deviation. The Shapiro–Wilk tests were used to assess normal distribution of variables, variables with non-normal distribution were expressed as median (IQR). One-way ANOVA and Kruskal–Wallis H-test were used to compare the differences of malnutrition phenotypes and depression indices among the SGA groups. The independent samples *t*-test and Mann–Whitney U-test were used to compare the differences of depression between different groups of malnutrition phenotypes. Categorical variables were described as frequencies and percentages, and comparisons between groups were performed using the chi-square and Fisher test. Spearman correlation analysis was used to test the association between depression index and malnutrition phenotype. All tests were two-sided, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Characteristics related to malnutrition phenotypes

Data of 53 inpatients with malnutrition indicators were successfully collected in this pilot study. According to the SGA

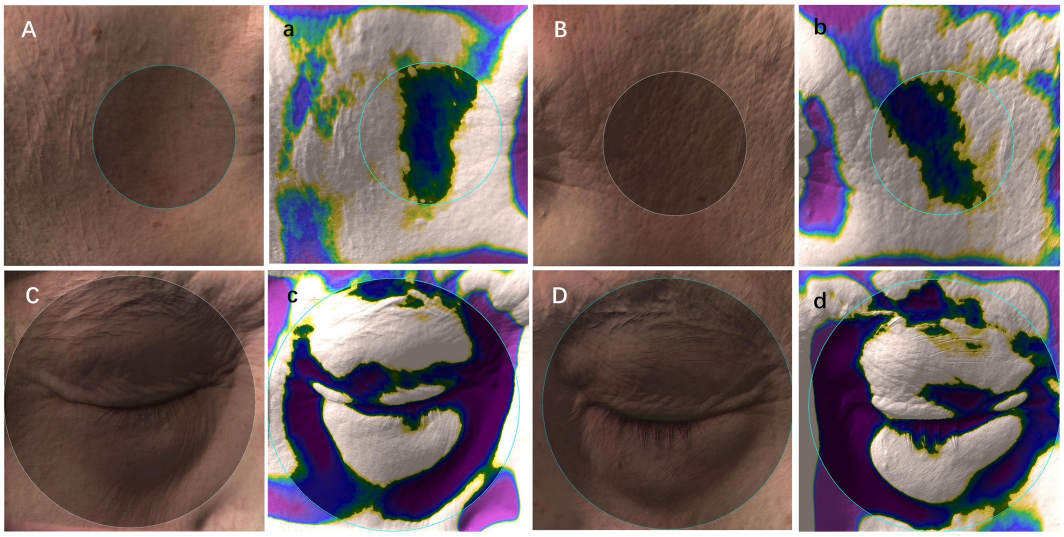

FIGURE 1
Schematic diagram of 3D image recognition and depression index acquisition. **(A–D)**: skin images; **(a–d)**: depression index sampling (gray region, the reference level; green, blue, and purple regions, depressions); Note: the circle indicated the pre-specified target area to obtain the quantitative data of depression volume, affected area, and maximum depth of temporal (diameter=30.8mm) and periorbital (diameter=54.1mm).

TABLE 1 Basic characteristics of malnutrition phenotypes in the study population.

Phenotypic characteristics	SGA A (*N*=30)	SGA B (*N*=15)	SGA C (*N*=8)	*p*-value
	Mean±SD / Median(IQR)	Mean±SD / Median(IQR)	Mean±SD / Median(IQR)	
Age (years)	57.70 ± 10.67	62.47 ± 9.32	55.25 ± 13.01	0.237
Sex (male, %)	18 (60)	13 (87)	6 (75)	0.197
Tumor location (gastrointestinal tract, %)	21 (70)	12 (80)	6 (75)	0.907
BMI (kg/m^2)	24.12 ± 2.99	23.07 ± 2.86	18.84 ± 2.69	<0.001***
AC (cm)	28.50 (4.10)	29.00 (4.00)	24.50 (3.00)	0.006**
CC (cm)	36.95 ± 2.26	35.58 ± 3.21	32.73 ± 4.38	0.003**
HGS (kg)	26.75 ± 7.64	28.77 ± 6.83	29.5 ± 11.35	0.587
FFMI (kg/m)	18.44 ± 2.30	18.49 ± 1.66	16.37 ± 2.45	0.051
FAT (kg)	16.05 ± 7.19	13.35 ± 6.33	6.99 ± 2.07	0.004**
FMI (kg/m)	5.68 ± 2.62	4.59 ± 2.08	2.47 ± 0.70	0.003**
VFA (kg)	54.15 (54.50)	42.00 (49.50)	31.20 (7.00)	0.072
PBF (%)	23.03 ± 9.14	19.29 ± 6.98	13.09 ± 3.25	0.009**

One-way ANOVA, Kruskal–Wallis H-test (AC, VFA), Fisher test (Sex, Tumor location): *$p<0.05$, **$p<0.01$, ***$p<0.001$. AC, arm circumference; CC, calf circumference; FAT, fat mass; FFMI, fat-free mass index; FMI, fat mass index; HGS, hand grip strength; PBF, percent body fat; VFA, visceral fat mass.

assessment, 30 patients had no risk of malnutrition (SGA A), 15 had mild-to-moderate malnutrition (SGA B), and 8 had severe malnutrition (SGA C). The distribution of clinical characteristics and malnutrition-related phenotypes among groups are presented in Table 1. Age, sex, and tumor location were evenly distributed among theree groups. In addition to most of the tumors located in the gastrointestinal tract (74%), a few patients were in the liver (4%), biliary tract (4%), pancreas (4%), etc. Except for HGS, FFMI, and VFM, measured malnutrition phenotypes (including BMI, AC, CC from physical examination, and FAT, FMI, and PBF measured by body composition analysis) were significantly different, and showed a downward trend along with the grade of malnutrition.

3.2. 3D facial image recognition depression indicators and SGA

In the temporal region, the volume (SGA A: 71.05 ± 27.20 mm^3, SGA B: 75.59 ± 31.72 mm^3, SGA C: 99.66 ± 38.34 mm^3, $p=0.068$) and surface area (SGA A: 244.71 ± 63.41 mm^2, SGA B: 259.21 ± 74.59 mm^2,

TABLE 2 Depression index differences among malnourished groups.

Depression index	SGA A (*N*=30)	SGA B (*N*=15)	SGA C (*N*=8)	*p*-value
	Mean±SD / Median(IQR)	Mean±SD / Median(IQR)	Mean±SD / Median(IQR)	
TEM-volume (mm^3)	71.05 ± 27.20	75.59 ± 31.72	99.66 ± 38.34	0.068
TEM-area (mm^2)	244.71 ± 63.41	259.21 ± 74.59	315.10 ± 84.66	0.049*
TEM-depth (mm)	0.60 (0.42)	0.56 (0.52)	0.68 (0.47)	0.760
ORB-volume (mm^3)	703.37 ± 145.48	784.73 ± 160.57	737.88 ± 140.92	0.234
ORB-area (mm^2)	1,061.09 ± 104.79	1,102.53 ± 98.07	1,108.63 ± 98.95	0.312
ORB-depth (mm)	2.46 ± 0.49	2.56 ± 0.40	2.39 ± 0.35	0.641

One-way ANOVA, Kruskal–Wallis H-test (TEM-depth): *$p<0.05$, **$p<0.01$, ***$p<0.001$. ORB, periorbital region; TEM, temporal region.

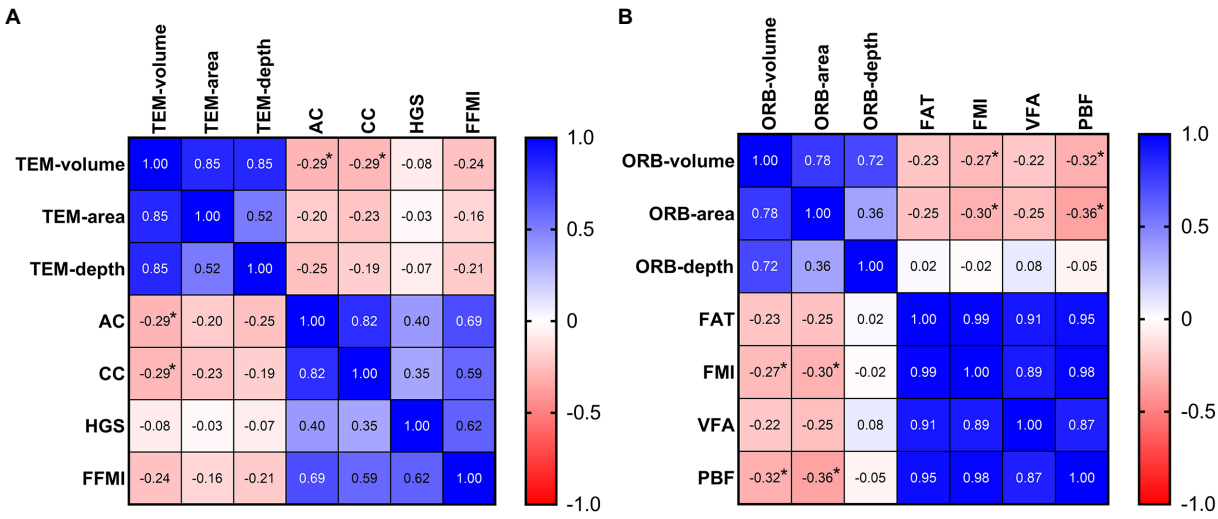

FIGURE 2
The correlation heatmaps between depression index and malnutrition phenotype. **(A)** The negative correlation between the temporal depression volume and muscle mass phenotype (AC and CC). **(B)** The negative correlation between the periorbital depression index (volume and surface area) and fat mass phenotype (FMI and PBF). AC, arm circumference; CC, calf circumference; FAT, fat mass; FFMI, fat-free mass index; FMI, fat mass index; HGS, hand grip strength; ORB, periorbital region; PBF, percent body fat; TEM, temporal region; VFA, visceral fat mass. Spearman correlation analysis: *$p<0.05$.

SGA C: 315.10 ± 84.66 mm^2, $p=0.049$) of depression showed a significant grading trend among dystrophic groups; the more severe the degree of malnutrition, the larger the volume or surface area of depression. No significant differences were found among the groups with respect to the maximum depth of depression (Table 2).

In the periorbital region, the surface area of periorbital depressions also showed a significant grading trend among the three groups. Patients in the SGA A group had the minimum affected area (1,061.09 ± 104.79 mm^2), followed by the SGA B group (1,102.53 ± 98.07 mm^2), while SGA C patients showed the largest depression (1,108.63 ± 98.95 mm^2). No obvious trends were found in the volume or maximum depth of periorbital depression among the groups (Table 2).

3.3. 3D facial image recognition depression indicators and malnutrition phenotypes

The volume of temporal depression was significantly negatively correlated with the upper AC ($r=-0.293$, $p=0.033$) and CC ($r=-0.285$, $p=0.038$). A larger upper AC or CC implies higher muscle mass and was found to be related to smaller volume of temporal depressions, while the phenotypes related to muscle mass, including HGS and FFMI, also exhibited a negative correlation with measures of temporal depression; however, the result was not statistically significant (Figure 2A).

The volume and surface area of the periorbital depressions were significantly negatively correlated with the FMI (volume: $r=-0.273$, $p=0.048$; surface area: $r=-0.304$, $p=0.026$) and PBF (volume: $r=-0.317$, $p=0.021$; surface area: $r=-0.364$, $p=0.007$). Both FMI and PBF are indicators of body fat content, and patients with more body fat exhibited smaller volume and surface area of periorbital depression. Moreover, FAT and VFM showed a negative correlation with the indices of periorbital depression; however, the difference was not statistically significant (Figure 2B).

Among the groups categorized based on the indicators of malnutrition phenotype, the volume and surface area of temporal depression in patients with muscle loss phenotypes (low AC/low CC/low HGS/low FFMI) were significantly higher than those in patients without muscle loss. Patients with the fat mass loss phenotype (low

TABLE 3 Depression index differences among various malnutrition phenotype groups.

Phenotype	Group (number)	TEM-volume (mm^3)		TEM-area (mm^2)		TEM-depth (mm)	
		Mean±SD/ Median (IQR)	*p*-value	Mean±SD/ Median (IQR)	*p*-value	Median (IQR)	*p*-value
AC (cm)	$M<27$, $F<25$ (14)	93.92 ± 31.11	0.015*	300.95 ± 74.49	0.011*	0.68 (0.46)	0.204
	$M>27$, $F>25$ (39)	70.45 ± 29.36		244.53 ± 67.09		0.58 (0.48)	
CC (cm)	$M<33$, $F<32$ (7)	100.26 ± 32.16	0.031*	358.51 (127.51)	0.024*	0.67 (0.45)	0.546
	$M>33$, $F>32$ (46)	73.06 ± 29.93		242.14 (102.98)		0.60 (0.42)	
HGS (kg)	$M<28$, $F<18$ (16)	89.17 ± 31.58	0.055	289.2 ± 65.88	0.049*	0.72 (0.49)	0.215
	$M>28$, $F>18$ (37)	71.24 ± 30.03		246.57 ± 72.76		0.60 (0.41)	
FFMI (kg/m)	M < 17, $F<15$ (10)	103.13 ± 35.03	0.002**	313.4 ± 84.09	0.008**	0.87 (0.47)	0.059
	M > 17, $F>15$ (43)	70.49 ± 27.32		246.89 ± 64.81		0.58 (0.33)	
Phenotype	Group (number)	ORB-volume (mm^3)		ORB-area (mm^2)		ORB-depth (mm)	
		Mean±SD	*p*-value	Mean±SD	*p*-value	Mean±SD	*p*-value
FMI (kg/m)	M < 7.7, $F<5$ (14)	761.37 ± 156.36	0.003**	1,106.34 ± 100.56	0.001**	2.48 ± 0.47	0.977
	M > 7.7, $F>5$ (39)	648.69 ± 96.25		1,006.60 ± 67.83		2.47 ± 0.40	

Independent sample *t*-test, Mann–Whitney U-test (CC&TEM-area, TEM-depth): *$p<0.05$, **$p<0.01$, ***$p<0.001$. AC, arm circumference; CC, calf circumference; FFMI, fat-free mass index; FMI, fat mass index; HGS, hand grip strength; ORB, periorbital region; TEM, temporal region.

FMI) also showed a significant increase in the volume and surface area of periorbital depression. The maximum depth of temporal and periorbital depression showed consistent trends between the groups; however, it was not statistically significant (Table 3).

4. Discussion

Our study has provided further evidence to support the association between face-specific depression indicators and dystrophic phenotypes. In particular, the degree of temporal depression was inversely correlated with the level of body muscle mass, and the degree of periorbital depression was negatively correlated with the level of subcutaneous fat mass. These findings were consistent with the results of nutritional physical examinations and suggest the application value of 3D image recognition of facial features in the diagnosis of malnutrition.

In our study, malnutrition-related phenotypes (anthropometric measures of muscle and fat mass) showed significant differences among patients with or without malnutrition; however, HGS, an indicator of muscle function, did not vary among groups. This indicates that although patients with cancer are at risk of muscle loss because of the inflammatory burden of tumor, they can still maintain a certain degree of muscle quality with active treatment and functional training (23), and thus reduce the adverse effects of malnutrition. Moreover, the differences between manually measured phenotypic indicators and objective indicators measured by body composition analysis suggest possible sensitivity differences between subjective malnutrition assessment and objective nutritional status (24), indicating the importance of a standardized malnutrition diagnosis.

In the nutrition-focused physical assessment (NFPA) proposed by the American Academy of Nutrition and Dietetics and ASPEN (25), the amount of temporal muscles was identified as an evaluation indicator for changes in body muscle mass. Recent studies have confirmed the association between temporal muscle thickness (measured using ultrasound (26) or CT (27)) and muscle mass, energy expenditure (28), or nutritional status. This is consistent with our study findings, indicating an association between temporal muscle atrophy-related depression indices and body muscle loss or malnutrition. However, our study did not find the correlation between temporal depressions and handgrip strengths, which might be due to the inconsistency between muscle quality and muscle mass in our participants, and suggested that the function of upper limb muscle may not be related to the volume of facial muscle.

Moreover, the NFPA guidelines use the periorbital fat pad as an important phenotypic indicator to evaluate the level of subcutaneous fat. Our study confirmed the consistency between the degree of periorbital depression and change in body fat mass, However, the thickness of the periorbital fat pad was also affected by age (29), sex (30), diseases (31), and other factors, which may explain the reason for no significant differences being observed in the periorbital depression indicators among patients with malnutrition of different grades. Our study also showed that the decrease of body fat had limited effect on the depth of periorbital depression, and the volume and surface area of periorbital depression should be taken into account when evaluating the periorbital fat pad. In addition, our study indicated that periorbital depressions mainly reflected changes in subcutaneous fat mass, and its relationship with VFM requires further research.

Computer-assisted image recognition technology has been widely used in many diseases, including cardiovascular diseases (32), digestive system diseases (33), and skin lesions (34), 3D facial imaging can not only quantify facial features comprehensively and accurately but is also favored by many mobile phone programs because of convenient sampling and simplified technical difficulty (35). As a multi-system and multi-dimensional assessment, malnutrition

diagnosis has no unified and standard evaluation system. Thus, the promotion of malnutrition diagnosis in the clinical environment requires high cost on personnel training, and it is difficult to achieve consistency. In the future, the use of simple and fast 3D image recognition technology to obtain malnutrition characteristics, combined with machine learning technology to accurately identify malnourished patients, will help in early screening of malnutrition risk in preclinical settings and timely provision of interventions to improve its prognosis. This is one of the innovative ways for malnutrition assessment system to be effectively implemented in grass-roots medical and health institutions, such as community hospitals, nursing institutions and mental illness centers.

Our study also has some limitations. First, being a pilot study, the sample size was small; however, distribution of malnutrition among the included patients was consistent with the prevalence of malnutrition in hospitalized patients with cancer found in previous surveys, indicating that the study population was still representative to some extent. Second, we did not use the gold standard DXA, CT, and MRI for muscle mass measurement but instead used portable BIA, which reduced the accuracy of body composition measurement. However, BIA is more widely used in clinical settings, and the cost is relatively low, which is conducive to the promotion and verification of tests in a large population. Finally, the 3D image analysis method used in this study is relatively simple, and the accuracy and quantity of extracted data from facial features are limited, which may be the reason why we found that the correlation between facial depressions and malnutrition phenotype is relatively low (0.2–0.4). In a later study with an enlarged amount of facial image data, more image recognition and machine learning technologies will be introduced to improve the accuracy of facial recognition and malnutrition diagnosis, and to further verify the effectiveness of 3D facial image in the diagnosis of malnutrition.

5. Conclusion

The facial temporal region and periorbital depression indicators extracted by 3D image recognition technology were significantly associated with the phenotype of malnutrition-related muscle loss and fat loss and showed a trend of grade changes in the population of different SGA nutritional classifications. 3D facial image recognition technology is expected to become an important clinical auxiliary tool for extracting phenotypic indicators of malnutrition in the population and for early warning of malnutrition risk.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Peking Union Medical College Hospital (Number: JS-2768). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XL and WC equally contributed to the conception and design of the research. XW and MH contributed to the acquisition of the data. YL and NY contributed to the interpretation of the data. MC analyzed the data and drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved this statement.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of geriatric nutritional risk index with all-cause hospital mortality among elderly patients in intensive care unit

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Background: Malnutrition is associated with poor outcomes for geriatric patients in intensive care unit (ICU). It is important to identify patients at risk of malnutrition and provide individual nutrition support. The assessment of malnutrition risk is not easy for these patients due to their cognitive impairment. Geriatric nutrition risk index (GNRI) is a simple and objective scoring tool to evaluate the risk of malnutrition in elderly patients. In this study, we aimed to see whether GNRI score was appropriate to predict clinical outcomes among geriatric patients in the setting of ICU.

Materials and methods: Elderly patients with age≥65years were extracted from Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Categories based on GNRI were classified as major risk (GNRI <82), moderate risk (GNRI 82 to <92), low risk (GNRI 92 to ≤98), and no risk (GNRI >98). The primary outcome was all-cause hospital mortality. Multivariable Cox proportional hazards regression models and restricted cubic spline were used to investigate associations of GNRI with hospital mortality, respectively. A two-piecewise linear regression model was applied to examine the inflection point of GNRI on hospital mortality. To reduce selection bias, propensity score matching (PSM) was used in a 1:1 ratio.

Results: A total of 3,696 geriatric patients were finally included with median age 75 (69, 81) years. The prevalence of major risk was 28.6%. In the fully adjusted model, GNRI categories featured a negative trend with hospital mortality (*p* for trend=0.037). Restricted cubic spline analysis demonstrated an L-shaped relationship between GNRI and hospital mortality before and after matching. The inflection point was 78.7. At the left side of inflection point, GNRI levels were significantly negatively associated with hospital mortality (HR=0.96, 95% CI: 0.94–0.98; $p<0.001$) and featured no significant relations at the right side. Multiple linear regression also showed that GNRI was negatively associated with length of stay in hospital.

Conclusion: The major risk of malnutrition defined by GNRI was able to predict poor prognosis for geriatric patients admitted to ICU.

KEYWORDS

geriatric nutritional risk index, malnutrition evaluation, hospital mortality, MIMIC-IV database, intensive care unit

1. Introduction

According to the population division of United Nation, the proportion of persons aged 65 or over is projected to increase globally between 2022 and 2050. The older population is estimated to reach 994 million by 2030 and 1.6 billion by 2050 (1). Malnutrition appears to be a common issue among older population with the aging process, ranging from 10 to 50% due to different diagnostic criteria (2). For hospitalized older patients, only 14% of them are nutritional well-being according to a multinational retrospective pooled analysis (3). For the critically ill geriatric patients in the intensive care unit (ICU), stress-related catabolism and proinflammatory cytokines might further result in deterioration of nutritional status after admission to ICU (4), which leads to prolonged length of stay, increased incidence of infection and poor prognosis (5). Therefore, it is important to identify elderly patients with malnutrition risk in a timely manner and treat them adequately so as to minimize the development of malnutrition and reduce its deleterious results.

However, dozens of nutrition screening tools have been proposed and there is no tool to be currently considered the gold standard for screening risk of malnutrition (6). Mini Nutritional Assessment (MNA) is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) (7). While, Nutritional Risk Screening-2002 (NRS-2002) and Nutrition Risk in the Critically ill (NUTRIC) score are suggested by The American Society for Parenteral and Enteral Nutrition (ASPEN) (8). However, these tools have limitations for clinical application. First, these assessments require a series of questionnaires, which are too complex to be suitable for older patients with difficulties in communication and cooperation. Besides, Acute Physiology and Chronic Health Evaluation II (APACHEII) score are necessary for NRS-2002 and NUTRIC score, which impedes screening due to spending a lot of time and effort (9). So, it is necessary to find a rapid, simple and objective tool that allows clinicians to screen for malnutrition risk among older individuals admitted to ICU.

Geriatric nutritional risk index (GNRI) was developed by Bouillanne et al. in 2005 and was designed specifically to assess nutritional status of the aging population (10). The calculation of GNRI is based on serum albumin level and body mass index (BMI). Several studies have validated that low GNRI score was associated with poor prognosis in patients with heart failure (11), acute coronary syndrome (12), chronic hemodialysis (13), malignancy (14), and acute ischemic stroke (15). However, the association between GNRI and prognosis in ICU is limited. In this study, we aimed to investigate whether GNRI score was able to predict clinical outcomes among geriatric patients in the setting of ICU.

2. Materials and methods

2.1. Data source

We conducted this retrospective study based on Medical Information Mart for Intensive Care IV version 1.0 (MIMIC-IV v1.0) database. MIMIC-IV, a large and public database, contains comprehensive data of more than 60,000 patients admitted to the ICU at Beth Israel Deaconess Medical Center from 2008 to 2019 (16). One author (P.J.C) has completed the online training course of the National Institutes of Health and obtained access to the database (record ID: 41046393). The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

2.2. Study population and group stratification

The inclusion criteria included: (1) age $\geq$ 65; (2) length of stay in ICU $\geq$ 24 h. Patients with missing key data (height, weight or albumin) on the first day of admission were excluded from the study. For patients with multiple hospitalizations, we only used their first hospitalization. The GNRI was calculated with the following formula (10): GNRI = 1.489 $\times$ serum albumin (g/L) + 41.7 $\times$ present weight (kg)/ideal weight (kg). The ideal body weight was calculated according to the Lorentz equations (10): 0.75 $\times$ height (cm) – 62.5 for men and 0.60 $\times$ height (cm) – 40 for women. When present weight exceeded ideal weight, present weight/ideal weight was set to 1. Patients were stratified into four groups according to the GNRI values, namely, major risk (GNRI: <82), moderate risk (GNRI: 82 to <92), low risk (GNRI: 92 to $\leq$98), and no risk (GNRI: >98) (10).

2.3. Outcome

The primary outcome was all-cause mortality in hospital. The secondary outcomes included ICU mortality, length of stay (LOS) in ICU and LOS in hospital.

2.4. Data extraction

The PostgreSQL 10.7 software and Structured Query Language were used to extract the baseline data within the first 24 h of ICU admission from the MIMIC-IV database. The following variables were collected, (1) demographic characteristics (age, gender, height, weight); (2) laboratory indicators (white blood cell (WBC) count, platelet count, hemoglobin, alanine transaminase (ALT), aspartate aminotransferase (AST) international normalized ratio (INR), serum creatinine (sCr), blood urea nitrogen (BUN), serum sodium, serum potassium, serum chloride, bicarbonate, anion gap and lactate); (3) comorbidities were identified according to International Classification of Diseases, 9th revised (ICD-9) and 10th revised (ICD-10) editions (chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), myocardial infarction (MI), chronic kidney disease (CKD), cirrhosis, cerebral infarction, malignancy and sepsis); (4) clinical severity scales (Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score II (SAPS II)); (5) treatment measures (renal replacement therapy (RRT) and mechanical ventilation (MV)).

2.5. Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) for normal distribution and as the median and interquartile range (IQR) for skewed distribution. Normal distributions were confirmed by Shapiro–Wilk test. Continuous

variables were compared by one-way ANOVA or Kruskal-Wallis H test, respectively. Categorical variables were compared using the χ^2-test or Fisher exact test as appropriate.

Multivariable Cox proportional hazard models were used to examine the hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between predefined GNRI groups and mortality. Model 1 was adjusted for age, gender and laboratory indicators. Model 2 was adjusted for variables in model 1 plus comorbidities and treatment measures. Model 3 was adjusted for variables in model 2 plus clinical severities. The assumption of the proportional hazards analysis was confirmed graphically by log cumulative hazard plots for mortality based on GNRI category. *p* for trend test was conducted by including the levels of GNRI as an ordinal score to the regression models. Restricted cubic spline (RCS) is a powerful tool to characterize a dose–response association between a continuous exposure and an outcome. RCS divide the observed range of the continuous variable with k knots and create a third order polynomial above the knot. RCS fit smoothly at each knot and to be linear both below the first knot and above the last knot. The knots are usually located at fixed percentiles of the continuous variable (17). So, the associations between continuous scale of GNRI and mortality were evaluated by RCS based on Cox proportional hazard models with three knots at the 10th, 50th and 90th percentiles of the distribution, adjusting for covariates in Model 3. The functional form of associations was evaluated by a Wald test comparing a linear or nonlinear likelihood ratio. Results were reported in log-relative hazard ratios and associated 95% CIs. If there were nonlinearity, we would further apply a two-piecewise linear regression model to examine the inflection point of GNRI on mortality, which provided maximum model likelihood. Finally, propensity score matching (PSM) was used to reduce selection bias in observational studies (18). Patients were matched in a 1:1 ratio with a caliper of 0.1 standard deviations of the Cox of the estimated propensity score with hospital mortality. Confounding factors such as age, gender, laboratory indicators, comorbidities, clinical severity scales and treatment measures were selected for matching.

Multivariable linear regression was used to analyze the relationship between GNRI (both as continuous and categorical variables) with LOS in hospital and ICU. Subgroup analyses according to gender, COPD, CHF, MI, CKD, cirrhosis, cerebral infarction, malignancy, sepsis (as defined by the Sepsis-3 criteria (19)), RRT and MV were conducted to test their interactions with GNRI on primary endpoint. GNRI was standardized to a Z-score ((GNRI- mean value)/SD) in order to present the confidence intervals of each subgroup clearly.

All data analyses were performed using R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria) and a two-sided *p*-value < 0.05 was considered statistically significant for all analyses. Variables with missing values were imputed using the multiple imputation method.

3. Results

3.1. Baseline characteristics

According to the inclusion criteria, a total of 3,696 elderly patients were finally obtained in the study (Figure 1). The median age

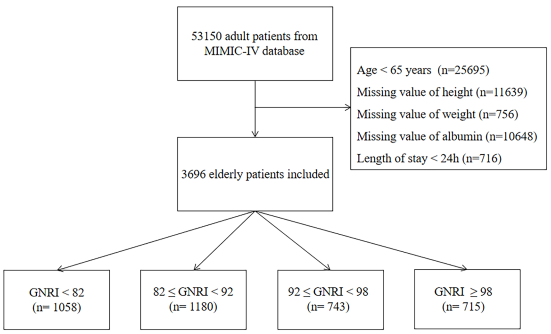

FIGURE 1
Flow chart of patients selection.

of enrolled patients was 75 (IQR, 69–81) years with 2,095 (55.9%) male patients. Based on GNRI stratification, 1058 (28.6%) patients were in major risk group, 1180 (31.9%) patients were in moderate risk group, 743 (20.1%) patients were in mild risk group and 715 (19.3%) patients were in no risk group. The baseline characteristics of study population stratified by GNRI were shown in Table 1. With the decreasing of GNRI, patients with nutritional risk in ICU tended to be older and more likely to be female. In terms of laboratory indicators, patients in major risk group featured higher levels of WBC count, ALT, AST, bilirubin, INR, creatinine, BUN, and lactate and lower levels of hemoglobin, platelet count and bicarbonate compared with patients in no risk group. The prevalence of cirrhosis, sepsis and malignancy were more common in patients in major risk group. RRT and MV were used more frequently in patients with major nutritional risk. Clinical severities increased significantly with the decreasing of GNRI. When compared with patients in no risk group, patients in major risk group had significantly higher hospital mortality (30.7 vs. 15.2%, $p < 0.001$) and ICU mortality (24.3 vs. 11.7%, $p < 0.001$), and longer LOS in ICU (4.3, IQR (2.3–8.6) vs. 3.4, IQR (2.0–6.4), $p < 0.001$) and LOS in hospital [10.0, IQR (6.0–17.0) vs. 7.0, IQR (5.0–13.0), $p < 0.001$].

3.2. Multivariable Cox regression analyses between GNRI and all-cause mortality

As shown in model 1, after adjusting for age, gender and laboratory indicators, multivariable Cox proportional hazard models demonstrated significant negative associations between GNRI categories and hospital mortality (major risk vs. moderate risk [HR = 0.79, 95% CI: 0.65–0.96]; vs. mild risk [HR = 0.74, 95%: CI 0.58–0.96]; vs. no risk [HR = 0.66, 95% CI: 0.49–0.88]; *p* for trend 0.002). In model 2, after adjusting for variables in model 1 plus comorbidities and treatment measures, GNRI categories still had significantly negative associations with all-cause hospital mortality (major risk vs. moderate risk [HR = 0.79, 95% CI: 0.65–0.96]; vs. mild risk [HR = 0.75, 95% CI: 0.58–0.97]; vs. no risk [HR = 0.66, 95% CI: 0.50–0.89]; *p* for trend 0.026). However, in model 3, after adjusting for variables in model 2 plus clinical severities, GNRI categories only featured negative trend with hospital mortality (*p* for trend 0.037). Besides, there were no significant correlations between GNRI categories and ICU mortality in model 3 (Table 2).

TABLE 1 Baseline characteristics of the study population grouped according to GNRI.

Characteristics	GNRI				*p*-value
	<82 (*n*=1058)	82 to <92 (*n*=1180)	92 to ≤98 (*n*=743)	>98 (*n*=715)	
Age	75.0 (69.0–81.0)	76.0 (70.0–81.0)	75.0 (70.0–81.0)	74.0 (69.0–80.0)	0.005
Male, *n* (%)	555 (52.5)	651 (55.2)	421 (56.7)	438 (61.3)	0.003[a]
Laboratory indicators					
WBC count (10^3/μl)	10.5 (6.8–15.1)	9.8 (7.1–13.5)	8.80 (6.7–11.8)	8.7 (6.7–11.3)	<0.001
Hemoglobin (g/dl)	8.8 (7.5–10.1)	9.7 (8.4–11.2)	10.3 (8.9–11.8)	11.1 (9.6–12.9)	<0.001
Platelet count (10^3/μl)	157.0 (99.0–238.0)	166.0 (115.0–232.2)	171.0 (127.00–227.5)	172.0 (134.0–220.0)	0.002
ALT (U/L)	33.0 (16.0–97.0)	28.0 (16.0–76.0)	23.0 (15.00–47.2)	22.0 (16.0–34.0)	<0.001
AST (U/L)	50.0 (28.0–146.00)	44.0 (26.0–121.5)	37.0 (23.0–76.0)	30.0 (22.0–52.0)	<0.001
Bilirubin (mg/dl)	0.8 (0.5–1.8)	0.7 (0.4–1.3)	0.6 (0.4–1.1)	0.6 (0.4–1.0)	<0.001
INR	1.5 (1.3–1.9)	1.3 (1.2–1.7)	1.3 (1.2–1.6)	1.2 (1.1–1.5)	<0.001
Creatinine (mg/dl)	1.4 (0.9–2.4)	1.4 (0.9–2.2)	1.2 (0.9–1.8)	1.1 (0.9–1.6)	<0.001
BUN (mg/dl)	34.0 (20.0–51.0)	29.0 (20.0–47.0)	24.0 (18.0–42.0)	23.0 (17.0–34.0)	<0.001
Bicarbonate (mmol/L)	19.0 (16.0–22.0)	21.0 (18.0–24.0)	21.0 (19.0–24.0)	22.0 (19.0–24.0)	<0.001
Anion gap (mmol/L)	17.0 (14.0–21.0)	17.0 (14.0–20.0)	16.0 (14.0–19.0)	17.0 (15.0–20.0)	0.357
Sodium (mmol/L)	140.0 (137.0–143.0)	140.0 (138.0–143.0)	140.0 (138.0–143.0)	140.0 (138.0–143.0)	0.207
Potassium (mmol/L)	4.6 (4.1–5.2)	4.5 (4.1–5.1)	4.5 (4.1–5.1)	4.5 (4.1–5.1)	0.310
Chloride (mmol/L)	103.0 (98.0–107.0)	102.0 (98.0–106.0)	102.0 (97.0–105.0)	101.0 (98.0–104.0)	<0.001
Lactate (mmol/L)	2.6 (1.6–5.4)	2.2 (1.4–4.0)	2.1 (1.3–3.5)	2.2 (1.6–3.6)	<0.001
Comorbidities, n (%)					
COPD	91 (8.6)	109 (9.2)	63 (8.5)	42 (5.9)	0.070[a]
CHF	318 (30.1)	472 (40.0)	301 (40.5)	213 (29.8)	<0.001[a]
MI	185 (17.5)	251 (21.3)	172 (23.1)	155 (21.7)	0.018[a]
CKD	193 (18.2)	242 (20.5)	140 (18.8)	110 (15.4)	0.049[a]
Cirrhosis	109 (10.3)	84 (7.1)	38 (5.1)	32 (4.5)	<0.001[a]
Cerebral infarction	43 (4.1)	44 (3.7)	45 (6.1)	51 (7.1)	0.002[a]
Malignancy	367 (34.7)	385 (32.6)	192 (25.8)	171 (23.9)	<0.001[a]
Sepsis	878 (83.0)	882 (74.7)	458 (61.6)	416 (58.2)	<0.001[a]
Clinical severities					
SOFA	5.0 (3.0–8.0)	4.0 (2.0–7.0)	3.0 (1.0–6.0)	2.0 (1.0–5.0)	<0.001
SAPS II	49.0 (40.0–59.0)	44.0 (36.0–52.0)	39.0 (32.0–48.0)	37.0 (30.0–45.0)	<0.001
Treatment, n (%)					
RRT	111 (10.5)	89 (7.5)	37 (5.0)	27 (3.8)	<0.001[a]
MV	708 (66.9)	713 (60.4)	395 (53.2)	376 (52.6)	<0.001[a]
Outcomes					
Hospital mortality, *n* (%)	325 (30.7)	259 (21.9)	130 (17.5)	109 (15.2)	<0.001[a]
ICU mortality, *n* (%)	257 (24.3)	199 (16.9)	109 (14.7)	84 (11.7)	<0.001[a]
LOS in hospital	10.0 (6.0–17.0)	9.0 (6.0–15.0)	7.0 (5.0–13.0)	7.0 (5.0–13.0)	<0.001
LOS in ICU	4.3 (2.3–8.6)	4.2 (2.1–7.7)	3.6 (2.0–6.3)	3.4 (2.0–6.4)	<0.001

Values were shown as median (interquartile range) unless otherwise indicated. ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GNRI, geriatric nutritional risk index; INR, international normalized ratio; LOS, length of stay; MI, myocardial infarction; MV, mechanical ventilation; RRT, renal replacement therapy; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.[a]$\chi 2$ -test.

3.3. Dose–response association between GNRI and all-cause mortality

On a continuous scale of GNRI, restricted cubic spline in a fully adjusted model showed that the associations of GNRI levels with all-cause hospital mortality (p for non-linearity = 0.003) and ICU mortality (p for non-linearity = 0.032) were L-shaped (Figure 2). The two-piecewise linear regression models indicated that the inflection points of GNRI for hospital and ICU mortality were 78.7 and 78.9, respectively. At the left side of inflection point, GNRI levels were

TABLE 2 Cox proportional hazard models of the relationship between GNRI and all-cause mortality.

Categories	Model 1*	*p* value	*p* for trend	Model 2†	*p* value	*p* for trend	Model 3‡	*p* value	*p* for trend
	HR (95% CIs)			HR (95% CIs)			HR (95% CIs)		
Hospital mortality									
Major risk	1.00		0.002	1.00		0.002	1.00		0.037
Moderate risk	0.79 (0.65, 0.96)	0.016		0.79 (0.65, 0.96)	0.020		0.83 (0.68, 1.02)	0.070	
Low risk	0.74 (0.58, 0.96)	0.021		0.75 (0.58, 0.97)	0.026		0.81 (0.63, 1.05)	0.117	
No risk	0.66 (0.49, 0.88)	0.005		0.66 (0.50, 0.89)	0.006		0.75 (0.56, 1.01)	0.059	
ICU mortality									
Major risk	1.00		0.024	1.00		0.016	1.00		0.141
Moderate risk	0.80 (0.65, 0.98)	0.035		0.81 (0.65, 0.99)	0.046		0.85 (0.68, 1.07)	0.161	
Low risk	0.75 (0.57, 0.98)	0.040		0.75 (0.57, 0.99)	0.038		0.83 (0.62, 1.10)	0.191	
No risk	0.71 (0.52, 0.97)	0.025		0.71 (0.52, 0.98)	0.028		0.81 (0.59, 1.13)	0.214	

*Model 1: adjusted for age and gender and laboratory indicators (WBC, hemoglobin, platelet count, ALT, AST, bilirubin, INR, sCr, BUN, bicarbonate, anion gap, sodium, potassium, chloride, and lactate).
†Model 2: adjusted for model 1 plus comorbidities (COPD, CHF, MI, CKD, cirrhosis, cerebral infarction, malignancy and sepsis) and treatment measures (RRT and MV).
‡Model 3: adjusted for model 2 plus clinical severities (SOFA and SAPS II).

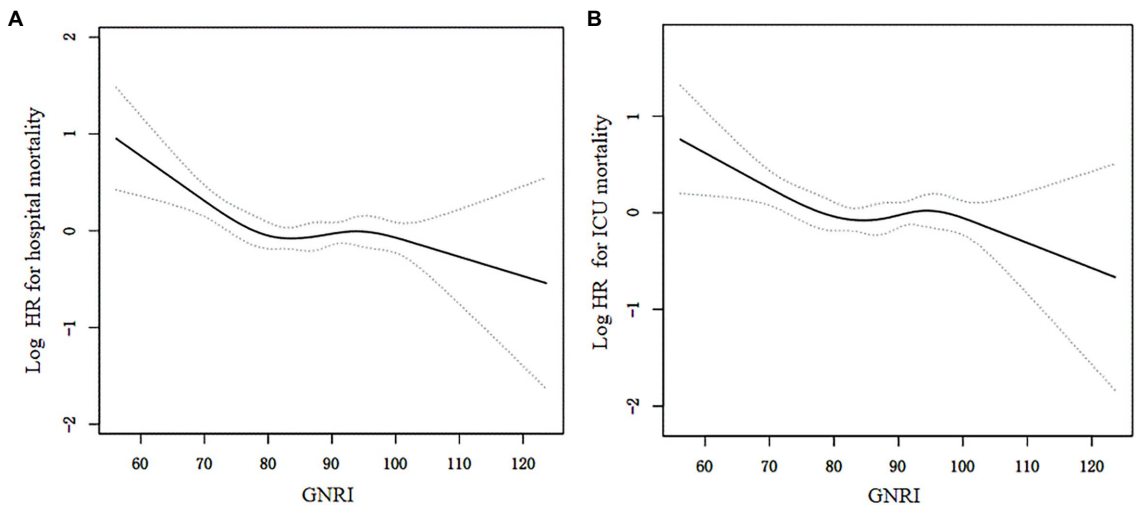

FIGURE 2
The associations of GNRI with hospital mortality **(A)** and ICU mortaltiy **(B)** by restricted cubic spline. The resulting figures showed the predicted log hazard ratios (HR) in the y-axis and the continuous levels of GNRI in the x-axis. The solid line represented the log hazard ratio and the dotted line was the 95% confidence interval (CI). HRs and associated 95% CIs were adjusted for variables in model 3.

significantly negatively associated with hospital mortality (HR = 0.96, 95% CI: 0.94–0.98; $p < 0.001$) and ICU mortality (HR = 0.97, 95% CI: 0.94–0.99; $p = 0.006$). While, at the right side of inflection point, GNRI levels had no significant relations with hospital or ICU mortality (Table 3).

After PSM, 778 patients in the non-survivor group were matched with 778 patients in the survivor group. The baseline profiles were well balanced between the two groups with standardized mean differences <10% for most of the variables (Additional file 1: Supplementary Table 1). Restricted cubic spline in a fully adjusted model also revealed an "L-shaped" relation (p for non-linearity = 0.004) between GNRI and hospital mortality (Additional file 1: Supplementary Figure 1).

3.4. Subgroup analyses of GNRI levels on hospital mortality

To further investigate possible interactions between GNRI levels and hospital mortality, several subgroup analyses were conducted according to gender, COPD, CHF, MI, CKD, cirrhosis, cerebral infarction, malignancy, sepsis, RRT and MV (Figure 3). After Z-transform standardization, significant interactions were observed in the subgroups of COPD (p for interaction =0.015) and malignancy (p for interaction =0.005). Elderly patients with COPD (HR = 0.62, 95% CI: 0.46–0.83; per unit increase in Z-score) and malignancy (HR = 0.74, 95% CI: 0.63–0.86; per unit increase in Z-score) featured stronger associations between GNRI levels and hospital mortality.

TABLE 3 Threshold effect of GNRI on all-cause hospital and ICU mortality.

	Hospital mortality	*p* value	ICU mortality	*p* value
Inflection point	78.7		78.9	
< Inflection point HR (95% CI)	0.96 (0.94, 0.98)	<0.001	0.97 (0.94, 0.99)	0.007
≥Inflection point HR (95% CI)	1.00 (0.99, 1.01)	0.814	1.00 (0.99, 1.01)	0.848
p for log likelihood ratio test		0.012		0.048

Data were presented as hazard ratios (HR) and 95% confidence intervals (CI). The two-piecewise linear regression models were adjusted for age, gender, laboratory indicators (WBC, hemoglobin, platelet count, ALT, AST, bilirubin, INR, sCr, BUN, bicarbonate, anion gap, sodium, potassium, chloride, and lactate), comorbidities (COPD, CHF, MI, CKD, cirrhosis, cerebral infarction, malignancy and sepsis), treatment measures (RRT and MV) and clinical severities (SOFA and SAPS II).

3.5. Relationship between GNRI and length of stay in hospital and ICU

As both category and continuous variables, multiple linear regression showed that GNRI was negatively associated with length of stay in hospital even after adjustment for age, gender and clinical severities among patients who were survival. However, after adjustment for age, gender and clinical severities, there was no significant relation between GNRI and length of stay in ICU (Table 4).

4. Discussion

GNRI was transformed from nutritional risk index (NRI), which was introduced by Buzby et al. in 1988 to evaluate the severity of postoperative complications and malnutrition in hospitalized adults (20). NRI consists of serum albumin concentration and weight loss. However, it is difficult for elderly patients to recall their usual weight. Hence, Bouillanne et al. replaced usual body weight with ideal body weight using the Lorentz formula and developed a novel nutritional index, namely GNRI (10). GNRI is a "nutrition-related" risk index rather than an index of malnutrition. So, GNRI can be used to classify patients according to a risk of nutrition-related mortality, not as a tool for grading nutritional status (10). In recent years, due to the development of nutritional support theory, emerging studies have found that GNRI was a useful tool to screen for malnutrition-related mortality among geriatric patients in different complications (11–15). However, as a novel nutritional index, the investigation of GNRI focusing on critically ill patients is limited. In daily practice, it is important for clinicians to identify high-risk malnutrition patients who would be more likely to get benefit from nutritional support. However, preexistence of cognitive impairment at ICU admission ranges from 6 to 42% among older patients (21, 22). It is impossible for these patients to complete a series of questionnaires which are needed by several evaluation tools, such as Subjective Global Assessment (SGA) and MNA (23). Other screening tools depend on weight and dietary changes, which are often difficult to obtain in ICU. So, compared with NRS-2002, NUTRIC score, SGA and MNA, GNRI is clearly simple, less time-consuming and requires minimal participation by patients.

In this retrospective study with a total of 3,696 geriatric patients, we investigated the relationship between GNRI score (at admission to ICU) and hospital mortality. The median age of included patients was 75 (IQR, 69–81). The prevalence of major malnutrition risk assessed by GNRI was 28.6%. Compared with patients in no risk group, patients in major risk groups had significantly higher ICU mortality, hospital mortality and longer duration of stay in ICU and hospital. This result was further supported by restricted cubic spline curves and we found an L-shaped association between continuous GNRI levels and the risk of all-cause mortality. Previous studies only investigated prognostic value of GNRI by focusing on specific ICU population, such as acute respiratory failure (9), stroke (24), and trauma (25). Therefore, the optimal cutoff value of GNRI suitable for general elderly patients remains to be elucidated. With the aid of two-piecewise linear regression models, we found that GNRI was significantly negatively associated with hospital mortality when it was less than 78.7 (HR = 0.96, 95% CI: 0.94–0.98) in the fully adjusted model. As mentioned with previous studies (26, 27), our study also found that GNRI had the ability to predict LOS in hospital. Therefore, elderly patients with malnutrition risk at admission to ICU tended to have a longer duration of stay in hospital.

Then, we further conducted subgroup analyses to find interaction effect and observed that GNRI featured a stronger relation with hospital mortality in patients with COPD or malignancy. For geriatric COPD patients, GNRI may be useful to be applied as a nutritional assessment scale (28, 29). As regard to malignancy, two meta-analyses concluded that low GNRI level was correlated with poor overall survival in patients with gastrointestinal malignancy (30) and lung cancer (31). Other studies also found its prognostic value in hepatocellular carcinoma (32), renal cancer (33), bladder cancer (34), and lymphoma (35, 36). Similarly, these results indicated clinical value of GNRI in nutrition assessment among elderly cancer patients.

Several limitations of this study should be considered. First, it was a single-center retrospective study. Prospective studies by multi-center are needed to validate the generalizability of the findings in the future. Second, the data were extracted from electronic database, missing important information in a certain of patients is evitable. Third, some useful indicators are incomplete, such as C-reactive protein (CRP), procalcitonin and B-type natriuretic peptide. So, these confounders were not adjusted in our model. Fourth, modified GNRI was developed recently by using the inverse of CRP instead of albumin (37). Due to the insufficient data of CRP, we were not able to make comparison of prognostic value between GNRI and modified GNRI. Last but not least, we did not make comparisons of diagnostic value among GNRI, NRS-2002, NUTRIC score, MNA and SGA. Further study needs to investigate which screening tool could provide more significant prognostic value in the critical care setting for elderly patients.

5. Conclusion

This study demonstrated that the associations of GNRI levels with hospital and ICU mortality were L-shaped. GNRI levels were negatively correlated with hospital and ICU mortality when its value was less than 79, which was slightly lower than that used for major risk. As a simple screening tool for malnutrition risk, the major risk of malnutrition defined by GNRI was able to predict poor prognosis for geriatric patients admitted to ICU, which allowed clinicians to identify suitable patients for nutritional support.

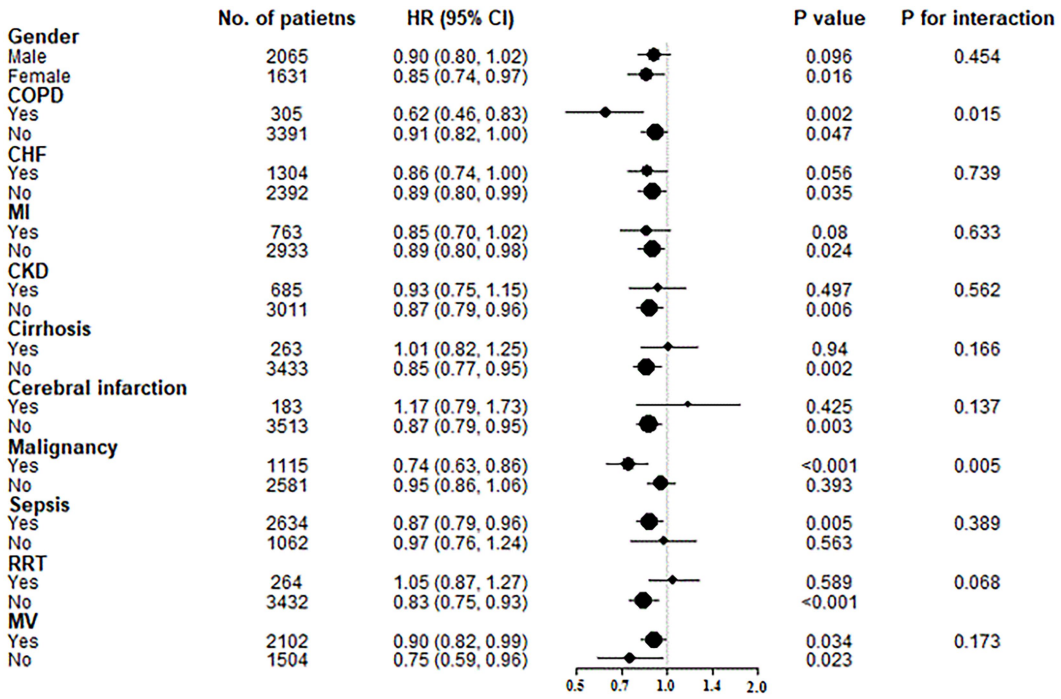

FIGURE 3
Subgroup analyses of the associations between GNRI levels and hospital mortality. GNRI was standardized to a *Z*-score. Above models were adjusted for variables in model 3. In each case, the model was not adjusted for stratification variable. COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; HI, myocardial infarction; CKD, chornic kidney disease; RRT, renal replacement therapy; MV, mechanical ventilation.

TABLE 4 Multivariable linear regression of the association between GNRI and length of stay.

	Length of stay in hospital[a]				Length of stay in ICU[b]			
	Crude model		Adjusted model*		Crude model		Adjusted model*	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
GNRI categories								
Major risk	1.00		1.00		1.00		1.00	
Moderate risk	−1.88 (−3.25, −0.51)	0.007	−0.73 (−2.08, −0.62)	0.291	−0.67 (−1.29, −0.04)	0.036	−0.07 (−0.68, 0.54)	0.823
Low risk	−4.06 (−5.58, −2.54)	<0.001	−1.94 (−3.47, −0.42)	0.012	−1.43 (−2.13, −0.74)	<0.001	−0.33 (−1.02, 0.37)	0.357
No risk	−3.96 (−5.49, −2.44)	<0.001	−1.60 (−3.15, −0.06)	0.042	−1.39 (−2.09, −0.69)	<0.001	−0.09 (−0.79, 0.62)	0.813
GNRI continuous								
GNRI levels	−0.18 (−0.23, −0.13)	<0.001	−0.09 (−0.14, −0.04)	<0.001	−0.06 (−0.09, −0.04)	<0.001	−0.01 (−0.04, 0.01)	0.253

*Adjusted for age, gender and clinical severities (SOFA and SAPS II).
[a]The association between GNRI and length of hospital stay was analyzed in patients who survived the hospital stay ($n = 2873$).
[b]The association between GNRI and length of ICU stay was analyzed in patients who survived the ICU stay ($n = 3047$).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

J-CP: writing—original draft preparation. Y-WZ: methodology. S-PX: validation. WL: formal analysis. YG: investigation. W-WG: writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1117054/full#supplementary-material

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Glossary

ALT	Alanine transaminase
APACHE	Acute physiology and chronic health evaluation II
ASPEN	American society for parenteral and enteral nutrition
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
ESPEN	European society for clinical nutrition and metabolism
GNRI	Geriatric nutritional risk index
HR	Hazard ratio
ICD	International classification of diseases
ICU	Intensive care unit
INR	International normalized ratio
IQR	Interquartile range
LOS	Length of stay
MI	Myocardial infarction
MIMIC-IV	Medical information mart for intensive care IV
MNA	Mini nutritional assessment
MV	Mechanical ventilation
NRS-2002	Nutritional risk screening-2002
NUTRIC	Nutrition risk in the critically ill
RRT	Renal replacement therapy
sCr	Serum creatinine
SAPS II	Simplified acute physiology score II
SGA	Subjective global assessment
SD	Standard deviation
SOFA	Sequential organ failure assessment
WBC	White blood cell

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Prognostic value of systemic immune inflammation index and geriatric nutrition risk index in early-onset colorectal cancer

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Background: Systemic nutritional and inflammatory markers, which are easy to measure are associated with the progression and prognosis of many cancers. Nevertheless, among the various available indicators, optimal prognostic indicators for patients with early-onset colorectal cancer have not been identified. Therefore, the aim of this study was to identify optimal nutritional and inflammatory markers for early-onset colorectal cancer and examine the relationship between systemic nutritional and inflammatory markers before treatment and survival in patients with early-onset colorectal cancer.

Methods: We retrospectively collected data from 236 eligible patients with early-onset colorectal cancer. Area under the prognostic curve (AUC) and concordance index (C-index) were used to compare seven systemic nutritional and inflammatory markers to identify the optimal inflammatory immune markers. Univariate and multivariate COX regression analyses were used to evaluate the prognostic value of indicators in the total study population and different subgroups.

Results: The AUC and C-index showed that the systemic immune inflammation index (SII) and geriatric nutrition risk index (GNRI) had higher prognostic values than other systemic nutritional and inflammatory indicators. Compared with patients in the low SII group, those in the high SII group had lower overall survival (HR, 4.42, 95% CI, 2.36–8.27, p=0.000). Compared with patients in the high GNRI group, those in the low GNRI group had lower overall survival (HR, 0.33, 95% CI, 0.19–0.56, p=0.000). SII was negatively associated with GNRI (R=–0.3, p<0.001), and both were correlated with the tumor stage.

Conclusion: SII and GNRI are suitable nutritional and inflammatory factors for predicting OS in patients with early-onset colorectal cancer; high SII and low GNRI were correlated with worse prognoses. Identifying the high inflammatory state and low nutritional state of patients before surgery and conducting active and timely therapeutic interventions could improve patient prognosis.

KEYWORDS

systemic inflammation, early-onset colorectal cancer, overall survival, SII, GNRI

1. Introduction

Colorectal cancer (CRC) is the fourth most deadly cancer globally, with almost 900,000 annual deaths (1). Due to the popularization of CRC screening in people over 50 years of age and lifestyle improvements, the overall incidence of and mortality from CRC have decreased by more than 45% since 1980 (2, 3). However, the incidence and mortality of colorectal cancer are increasing in adults aged 50 and younger (4, 5). Colorectal cancer diagnosed in people younger than 50 is generally considered early-onset, as screening programs begin at age 50 in most countries (6). Compared with late-onset colorectal cancer (older than 50 years), early-onset colorectal cancer presents with later stage tumors and unfavorable clinicopathological features; survival data on this group are currently lacking and contradictory (6). Analysis of the SEER database showed that younger patients are more prone to poorly differentiated, mucinous, and signet ring tumors than elderly patients (7). Although younger patients are more likely to receive neoadjuvant chemoradiotherapy and adjuvant chemotherapy, their disease-specific outcomes are comparable to those of older patients. This may be related to the unique biological and molecular characteristics of early-onset colorectal cancers (6, 8).

Increasing evidence has shown that inflammation is closely associated with cancer (9). McAllister and Weinberg (10) considered tumor-related systemic inflammation as the seventh feature of cancer, and only the "tip of the iceberg" in terms of cancer biology and treatment. All colorectal tumors that have been studied so far have been associated with the inflammatory environment. The inflammatory response plays a role in the entire process of tumorigenesis and cancer development. Inflammation induced by sporadic tumors can promote local tumor growth and distant metastases (9), which is generally reflected in increased levels of inflammatory cells and proinflammatory mediators. At the same time, pro-inflammatory cytokines produced by tumors will destroy the metabolism of carbohydrates, fats and proteins in the whole body, aggravate catabolism and lead to muscle decomposition. Combined with tumor consumption and insufficient nutrition intake, cancer patients have a high risk of malnutrition. Malnutrition can not only reduce the tolerance of cancer patients to anti-cancer treatment, including increasing the toxicity of treatment and impairing the quality of life, but also is closely related to the prognosis (11, 12). However, a recent European study found that only 30%–60% of cancer patients at risk of malnutrition received nutritional support treatment, meaning that many malnourished patients did not receive necessary nutritional interventions (13, 14). Hence, the search for nutritional and inflammatory biomarkers associated with poor prognosis is clinically important.

Systemic nutritional and inflammation response indicators are obtained by measuring clinical biochemical and hematological indicators. A variety of nutritional and inflammatory indicators including neutrophil-lymphocyte ratio (NLR) (15), platelet-lymphocyte ratio (PLR) (16), advanced lung cancer inflammation index (ALI) (17), systemic immune-inflammation index (SII) (18), geriatric nutrition risk index (GNRI) (19), prognostic nutritional index (20), and albumin to globulin ratio (AGR) (21) have been shown to be related to the prognosis of cancer. However, the prognostic role of these nutritional and inflammatory markers in early-onset CRC remains unclear.

Therefore, this study investigated optimal nutritional and inflammation indicators for early-onset colorectal cancer and examined the relationship between pre-treatment systemic nutritional and inflammatory indicators and survival rate. These factors are closely related to prognosis and could contribute to the risk stratification of patients.

2. Methods

2.1. Study population

We retrospectively collected data from patients younger than 50 years old at diagnosis who underwent radical resection of colorectal cancer in our hospital from December 2013 to December 2017. The inclusion criteria were as follows: (1) age at diagnosis between 18 and 49 years; (2) postoperative pathological diagnosis of adenocarcinoma; (3) had test indices before surgery or within 1 week before chemoradiotherapy. The exclusion criteria were as follows: (1) non-colorectal primary malignancy; (2) missing clinical data; (3) distant metastasis at the time of diagnosis. This study was approved by the Ethics Committee of our hospital. Informed consent was waived owing to the retrospective nature of the study.

2.2. Markers of systemic nutrition and inflammation

A variety of systemic nutritional and inflammatory markers that reportedly have prognostic value (all indicators were obtained within 1 week before surgery or other treatment) were retrospectively collected and calculated. The calculation formula was as follows. Inflammatory markers: NLR, neutrophil/lymphocyte (17); PLR, platelet/lymphocyte (16); ALI, BMI*albumin/NLR (17); SII, platelet*neutrophil/lymphocyte (18). Nutritional indices: GNRI, 1.489*albumin + 41.7*present body weight (PBW)/ideal body weight(IBW) (19); AGR, albumin/globulin (21); PNI, albumin+0.005*lymphocyte (20). BMI was defined as weight per height in meters squared. The IBW was defined as: for men = height − 100 − [(height − 150)/4]; for women = height − 100 − [(height − 150)/2.5].

2.3. Other covariates and end points

We also collected demographic information (age, gender, BMI, smoking history, drinking history), oncology information (tumor stage, tumor location, differentiation degree, nerve invasion status, vascular tumor thrombus), and treatment information (preoperative and postoperative radiotherapy and chemotherapy). Overall survival (OS) was the main study endpoint and was defined as the time between the initial diagnosis and death from any cause (the last follow-up was used for patients lost to follow-up; patients who were still alive at the end of the study were considered at the end of follow-up).

3. Statistics

SPSS 25.0 and R software (version 4.1.2) were used to analyze the data. Shapiro–Wilk test was used to test the normality of the distribution of continuous variables. Continuous variables were

described as mean plus standard deviation (SD) or median (Q1 to Q3), depending on their distribution. For normally distributed data, the difference between the two groups was evaluated using Student's t test, and the Mann–Whitney *U*-test was used otherwise. Categorical variables are presented as absolute numbers and percentages, and Fisher's exact test and Pearson's Chi-square test were used for comparisons between groups. The optimal cut-off value was calculated based on the maximally selected rank statistic in the "survminer" R package, which can determine the optimal cut-off value for one or multiple continuous variables at once. This is an outcome-oriented methods providing a value of a cut-off value that correspond to the most significant relation with outcome (here, overall survival). The best cut-off values of SII and GNRI were 637.6 and 83.13, respectively (Supplementary Figures S1, S2). The survival curve was drawn using the Kaplan–Meier method, and survival differences were compared using the Log-Rank test. Variables known to affect overall survival were included in the multivariate Cox proportional hazards model, and hazard ratios (HRs) and 95% confidence intervals were calculated. Three adjusted models were built: Model 0: unadjusted; Model 1: Adjusted for age, sex, BMI, and TNM stage; Model 2: Based on Model 1 and further adjusted for smoking status, alcohol consumption, tumor location, differentiation degree, nerve invasion status, vascular tumor thrombus, preoperative treatment, and postoperative treatment. An interaction $p < 0.1$ in the subgroup analysis was considered significant for the interaction. In other analyses, a two-sided $p \leq 0.05$ was considered statistically different.

4. Results

4.1. Patient characteristics

A total of 236 eligible patients were recruited into the study (Supplementary Figure S3). The median patient age was 45 years; 72 patients (30.5%) were younger than 40 and 164 patients (69.5%) were 40–49 years old. In this study, 1-, 3-, and 5-year survival rates were 91.3%, 76.5%, and 65.7%, respectively. All the patients included were Han nationality. The baseline patient characteristics are summarized in Table 1.

4.2. Selection of the best prognostic nutritional and inflammatory index

The optimal prognostic nutritional and inflammatory index in patients with early-onset colorectal cancer was selected through time-dependent ROC and concordance index (C-index). The results showed that SII and GNRI had higher prognostic values than other nutritional and inflammatory indicators; C-index and 95% CI were 0.692 (0.633–0.750) and 0.711 (0.652–0.770), respectively (Figure 1; Supplementary Table S1). Based on the SII cutoff value, all patients were divided into High SII and Low SII groups. The baseline characteristics are shown in Table 1. There were significant differences in gender, smoking status, alcohol consumption, tumor stage, and neurological invasion status, NLR, PLR, ALI, GNRI and AGR between the two groups (all $p \leq 0.05$). All patients were divided into High GNRI and Low GNRI groups based on the GNRI cut-off value. The baseline characteristics are shown in Table 1. Two groups had significant differences in gender, tumor stage, tumor differentiation, preoperative adjuvant therapy, postoperative adjuvant therapy, NLR, PLR and SII (all $p \leq 0.05$). We also observed a significant negative correlation between SII and GNRI ($R = -0.3$, $p < 0.001$; Supplementary Figure S4).

4.3. Prognostic value of SII and GNRI in early-onset colorectal cancer

Restricted cubic spline (RCS) was used to evaluate the relationship between SII, GNRI, and patient HR. The results indicated that with an increase in SII and a decrease in GNRI, patient HR gradually increased, suggesting that the risk of death gradually increased (Figures 2A,C). Consistent results were observed in the gender subgroups (Figures 2B,D). The box plot shows that as SII gradually increased, the tumor stage also increased (Figure 3A); GNRI gradually decreased with increasing tumor stage. There were statistical differences between stages 1 and 3, and stages 2 and 3 (Figure 3C). Consistent results were observed in the gender subgroups (Figures 3B,D), which may partially explain the relationship between SII, GNRI, and HR. The survival curve showed that compared to patients with low SII, those with high SII had a worse prognosis (Figure 4A, $P < 0.0001$). For every SD increase in SII, the risk of death increased 1.08-fold (Table 2, model 2, 95% CI = 1.05–1.11, $p = 0.000$). Compared to patients with low SII, the risk of death in patients with high SII increased 4.42-fold (model 2, 95% CI = 2.36–8.27, $p = 0.000$). Patients were divided into four groups (Q1: ~437.93; Q2: 437.93–691.19; Q3: 691.19–890.71; Q4: 890.71) according to the SII quartile value. The multivariate COX regression model showed that patients in the Q2 (model 2, HR = 4.09, 95% CI = 1.47–11.37, $p = 0.006$), Q3 (model 2, HR = 3.97, 95% CI = 1.45–10.86, $p = 0.007$) and Q4 (model 2, HR = 8.49, 95% CI = 3.22–22.36, $p = 0.000$) groups had an increased risk of death compared to those in the Q1 group. Sensitivity analysis results showed similar results, excluding patients who died within a year (Supplementary Table S2). However, patients with high GNRI had a better prognosis compared to those with low GNRI (Figure 4B, $P < 0.0001$). For each standard deviation increase in GNRI, the risk of death was reduced 0.97-fold (Table 3, model 2, 95% CI = 0.96–0.98, p = 0.000). Compared to patients with low GNRI, the risk of death in those with high GNRI was decreased 0.33 times (model 2, 95% CI = 0.19–0.56, $p = 0.000$). Patients were divided into four groups (Q1: ~91.50; Q2: 91.50–100.37; Q3: 100.37–107.64; Q4: 107.64) according to the GNRI quartile value. The multivariate COX regression model showed that patients in Q3 (model 2, HR = 0.29, 95% CI = 0.14–0.59, $p = 0.001$) and Q4 (model 2, HR = 0.29, 95% CI = 0.13–0.64, $p = 0.002$) groups had a lower risk of death compared with those in the Q1 group. After the exclusion of patients who died within a year, the results of the sensitivity analysis suggested a similar survival outcome (Supplementary Table S3).

Subgroup analysis of SII showed significant prognostic value in patients except for those aged <40 years, BMI 24–28, and BMI > 28 (Figure 5A). We also observed that GNRI had a significant prognostic value in patients aged 40–49 years, female, with a BMI between 18.5–24, and tumor stages II and III (Figure 5B). Furthermore, SII and GNRI showed good survival prediction in the BMI subgroups (18.5–24, 24–28, >28), gender (male, female), vascular tumor thrombus (positive, negative), neural invasion (positive, negative), preoperative

TABLE 1 Baseline characteristics of the study population.

Characteristics	Overall patients (*n*=236)	High SII (≥637.6) (*n*=132)	Low SII (<637.6) (*n*=104)	*P*-value	High GNRI (≥83.13) (*n*=203)	Low GNRI (<83.13) (*n* =33)	*P*-value
Age, M (Q1~Q3), y	45 (39–48)	45 (39.3–48)	45 (38.25–47)	0.648	45 (39–47)	45 (38.5–48.5)	0.609
Gender, *n* (%)				0.000*			
Male	143 (60.6)	66 (50.0%)	77 (74.0%)		131 (64.5%)	12 (36.4%)	0.002*
Female	93 (39.4)	66 (50.0%)	27 (26.0%)		72 (35.5%)	21 (63.6%)	
BMI, M (Q1~Q3), kg/m^2	22.9	22.3	23.3	0.051	22.8	24	0.119
	(20.8–25.6)	(20.5–25.0)	(21.2–26.3)		(20.8–25.1)	(20.8–27.7)	
BMI, *n* (%)				0.075			
<18.5	15 (6.4)	10 (7.6%)	5 (4.8%)		13 (6.4%)	2 (6.1%)	
18.5–24	139 (58.9)	83 (62.9%)	56 (53.8%)		124 (61.1%)	15 (45.5%)	0.123
24–28	58 (24.6)	24 (18.2%)	34 (32.7%)		49 (24.1%)	9 (27.3%)	
>28	24 (10.2)	15 (11.4%)	9 (8.7%)		17 (8.4%)	7 (21.2%)	
Smoking, *n* (%)				0.028*			
No	184 (78.0)	110 (83.3%)	74 (71.2%)		155 (76.4%)	29 (87.9%)	0.176
Yes	52 (22.0)	22 (16.7%)	30 (28.8%)		48 (23.6%)	4 (12.2%)	
Alcohol, *n* (%)				0.013*			
No	190 (80.5)	114 (86.4%)	76 (73.1%)		161 (79.3%)	29 (87.9%)	0.344
Yes	46 (19.5)	18 (13.6%)	28 (26.9%)		42 (20.7%)	4 (12.1%)	
Tumor stage, *n* (%)				0.017*			
I	32 (13.6)	13 (9.8%)	19 (18.3%)		32 (15.8%)	0 (0%)	0.000*
II	97 (41.1)	49 (37.1%)	48 (46.2%)		89 (43.8%)	8 (24.2%)	
III	107 (45.3)	70 (53.0%)	37 (35.6%)		82 (40.4%)	25 (75.8%)	
Tumor location, *n* (%)				0.761			0.155
Colon	141 (59.7)	80 (60.6%)	61 (58.7%)		125 (61.6%)	16 (48.5%)	
Rectum	95 (40.3)	52 (39.4%)	43 (41.3%)		78 (38.4%)	17 (51.5%)	
Differentiated degree, *n* (%)				0.359			
Poorly	75 (31.8)	47 (35.6%)	28 (26.9%)		59 (29.1%)	16 (48.5%)	0.032*
Moderately	153 (64.8)	81 (61.4%)	72 (69.2%)		138 (68.0%)	15 (45.5%)	
Well	8 (3.4)	4 (3.0%)	4 (3.8%)		6 (3.0%)	2 (6.1%)	

(Continued)

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TABLE 1 (Continued)

Characteristics	Overall patients (*n*=236)	High SII (≥637.6) (*n*=132)	Low SII (<637.6) (*n*=104)	*P*-value	High GNRI (≥83.13) (*n*=203)	Low GNRI (<83.13) (*n* =33)	*P*-value
Preoperative therapy, *n* (%)				0.061			
No	184 (78.0)	97 (73.5%)	87 (83.7%)		167 (82.3%)	17 (51.5%)	0.000*
Yes	52 (22.0)	35 (26.5%)	17 (16.3%)		36 (17.7%)	16 (48.5%)	
Postoperative therapy, *n* (%)				0.174			
No	41 (17.4)	19 (14.4%)	22 (21.2%)		41 (20.2%)	0 (0%)	0.002*
Yes	195 (82.6)	113 (85.6%)	82 (78.8%)		162 (79.8%)	33 (100%)	
Nerve invasion, *n* (%)				0.005*			0.165
Negative	156 (66.1)	77 (58.3%)	79 (76.0%)		138 (68.0%)	18 (54.5%)	
Positive	80 (33.9)	55 (41.7%)	25 (24.0%)		65 (32.0%)	15 (45.5%)	
Intravascular tumor emboli, *n* (%)				0.98			0.296
Negative	170 (72.0)	95 (72.0%)	75 (72.1%)		149 (73.4%)	21 (63.6%)	
Positive	66 (28.0)	37 (28.0%)	29 (27.9%)		54 (26.6%)	12 (36.4%)	
NLR, M (Q1~Q3)	2.49 (1.73–3.47)	2.88 (2.24–3.87)	1.94 (1.45–2.67)	0.000*	2.35 (1.69–3.31)	2.81 (2.39–4.23)	0.017*
PLR, M (Q1~Q3)	173.9	198.9	145.3	0.000*	169.1	247.6	0.004*
	(130.1–233.4)	(156.3–247.9)	(121.9–194.4)		(126.9–225.8)	(148.2–278.9)	
ALI, M (Q1~Q3)	44.3 (29.1–65.5)	36.0 (23.4–52.5)	59.7 (43.8–83.5)	0.000*	44.9 (29.1–67.1)	36.4 (24.9–57.5)	0.098
SII, M (Q1~Q3)	691.2 (437.1–891.1)	/	/	/	674.1 (405.7–862.0)	846.8 (594.5–1103.9)	0.010*
GNRI, M (Q1~Q3)	100.4 (91.4–107.7)	96.1 (87.3–104.5)	104.9 (96.5–110.6)	0.000*	/	/	/
AGR, M (Q1~Q3)	1.51 (1.28–1.71)	1.42 (1.21–1.66)	1.57 (1.38–1.75)	0.002*	1.51 (1.29–1.71)	1.42 (1.20–1.68)	0.449
PNI, M (Q1~Q3)	49.4 (43.5–55.4)	48.6 (43.4–56.8)	50.3 (44.3–54.9)	0.842	49.4 (43.5–55.2)	48.0 (43.6–62.8)	0.858

M (Q1~Q3), median (Q1~Q3); BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; GNRI, geriatric nutrition risk index; AGR, albumin to globulin ratio; PNI, prognostic nutritional index. *$p \leq 0.05$.

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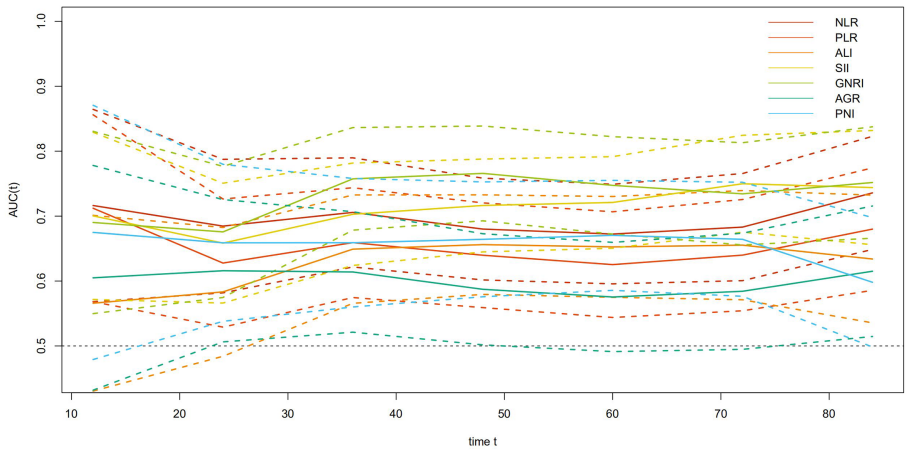

FIGURE 1
Time-dependent ROC for the seven immune-inflammatory markers.

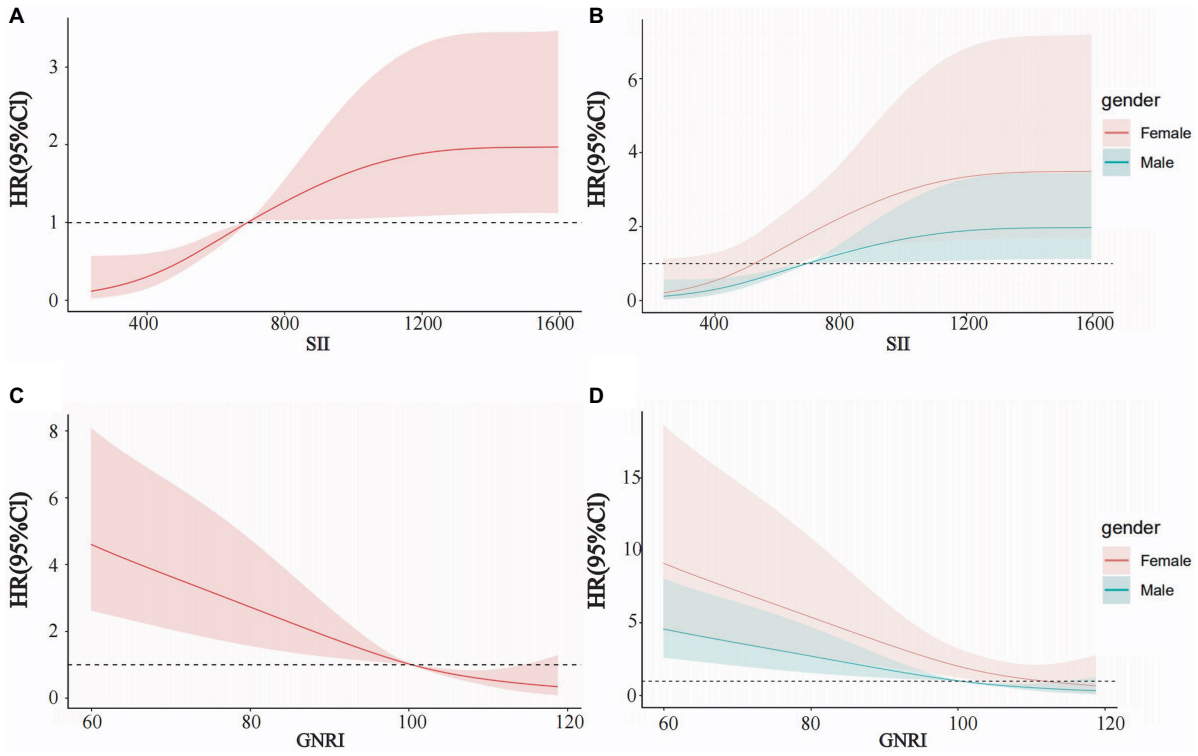

FIGURE 2
Restricted cubic spline curves for SII and GNRI in EOCRC. **(A)** SII in all patients, **(B)** SII in males and females, **(C)** GNRI in all patients, and **(D)** GNRI in males and females.

adjuvant therapy (yes, no), and postoperative adjuvant therapy (yes; Supplementary Figures S5, S6).

5. Discussion

Previous studies have shown that inflammatory mediators secreted due to chronic inflammation and related immune cells support the establishment and progression of tumors by inducing neoplastic mutations, increasing the proliferation rate of tumor cells, stimulating angiogenesis, and recruiting fibroblasts and other stromal cells (22–24). Some evidence is mounting that aspirin can reduce the incidence and growth rate of several cancers in animal models, mediated in part by the inhibition of COX-2 and a reduction in prostaglandins and other inflammatory mediators (25, 26). Notwithstanding various systemic

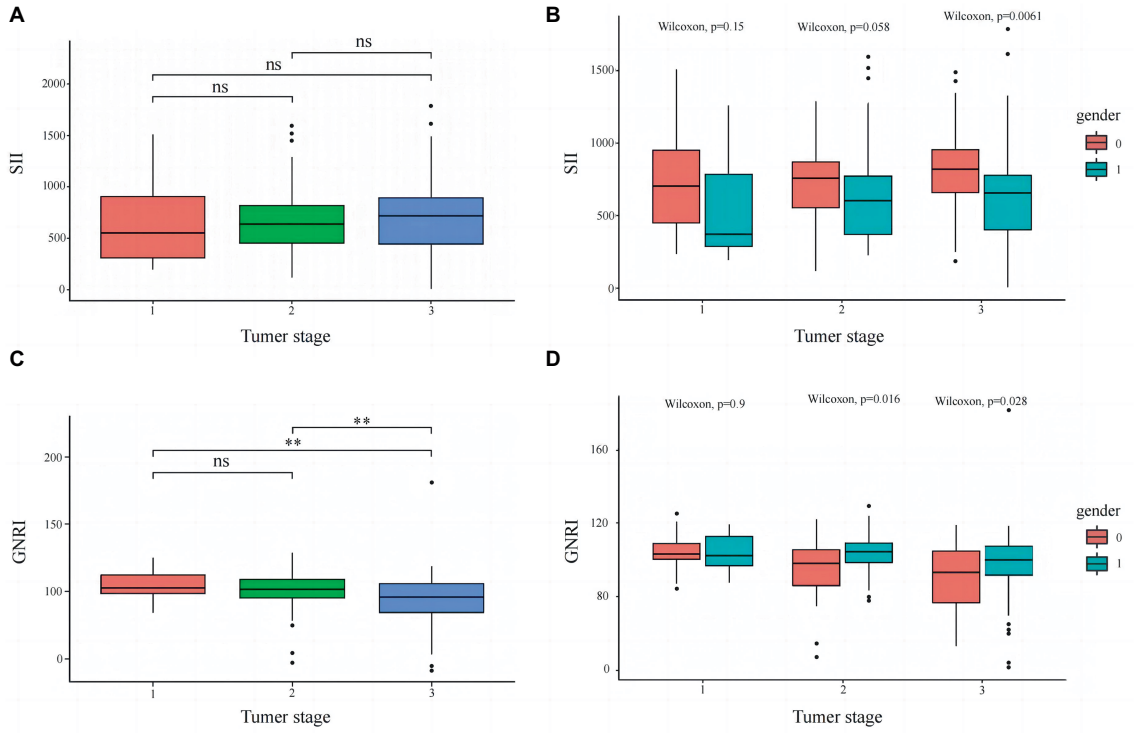

FIGURE 3
Distribution of SII and GNRI in different tumor stages. **(A)** SII in all patients, **(B)** SII in males and females, **(C)** GNRI in all patients, and **(D)** GNRI in males and females. $^{**}p \leq 0.05$.

inflammatory response (SIR) indicators reportedly related to cancer prognosis, optimal indicators in patients with early-onset colorectal cancer remain unclear. Our study found that SII and GNRI have potential prognostic value in patients with early-onset colorectal cancer.

Previous studies have shown that high SII is associated with poor prognosis in a variety of solid tumors (27–29). The formula for SII includes platelets, neutrophils, and lymphocytes. Increased SII generally reflects increased platelets and neutrophils or decreased lymphocytes, and its prognostic effect can be explained by the role each of these immune cells plays. Neutrophils recruited to inflammatory areas increase DNA damage and angiogenesis by producing large amounts of ROS, reactive nitrogen species (RNS), and MMP-9. Additionally, neutrophils suppress T cell viability through arginine depletion via arginase 1 (ARG1) and downregulation of CD3ζ (30). Moreover, neutrophils can also recruit macrophages and Tregs to promote tumor progression (31). Tumor necrosis factor (TNF) and cathepsin G derived from neutrophils promote distant metastasis of malignant tumors (32). Recently, studies have shown that platelets are not only the main cellular components of blood clots but also play an essential role in cancer growth and dissemination. Platelets are recruited to the tumor microenvironment to promote tumor-related blood coagulation, covering the tumor surface to protect tumor cells from the immune response. Related experiments have affirmed that specific blocking of platelet receptors such as GP1b/IX/V, GPIIbIIIa, and GPVI reduces the occurrence of metastasis (33). Lymphocytes, the most important immune cells in the body, play an anti-tumor role mainly by inducing lysis and apoptosis of target cells (34). During an inflammatory response, neutrophils suppress the immune system by inhibiting the cytolytic activity of lymphocytes, activated T cells, and natural killer cells. The lower the lymphocyte level, the worse the immune function. Isabelle et al. demonstrated that lymphopenia is an independent prognostic factor for overall and progression-free survival in a variety of cancers (35). Moreover, we found that with an increase in the tumor stage, the level of SII gradually increased; this trend was observed in both genders. NLR also showed relatively good predictive capacity in our study (AUC = 0.666). However, the predictive capacity of NLR was not as effective as that of SII. Compared with NLR, SII contains three types of inflammatory cells, more comprehensively reflecting the relationship between inflammation and immunity. Hence, an increase in SII indirectly reflects a decline in host immune function and increased tumor invasiveness (36).

GNRI is an indicator of nutritional status based on albumin, current body weight, and ideal body weight. It simulates changes in body weight through the ratio of current body weight to ideal body weight. GNRI was originally designed for elderly patients but is also suitable for young adults (37–39). Preoperative malnutrition is highly prevalent in patients with gastrointestinal (GI) cancer and can lead to increased postoperative complications, longer hospital length of stay (LOS), and worse prognosis (40, 41). Therefore, it is necessary to evaluate and improve the nutritional status of patients before treatment. Albumin is synthesized in the liver, and low albumin levels are

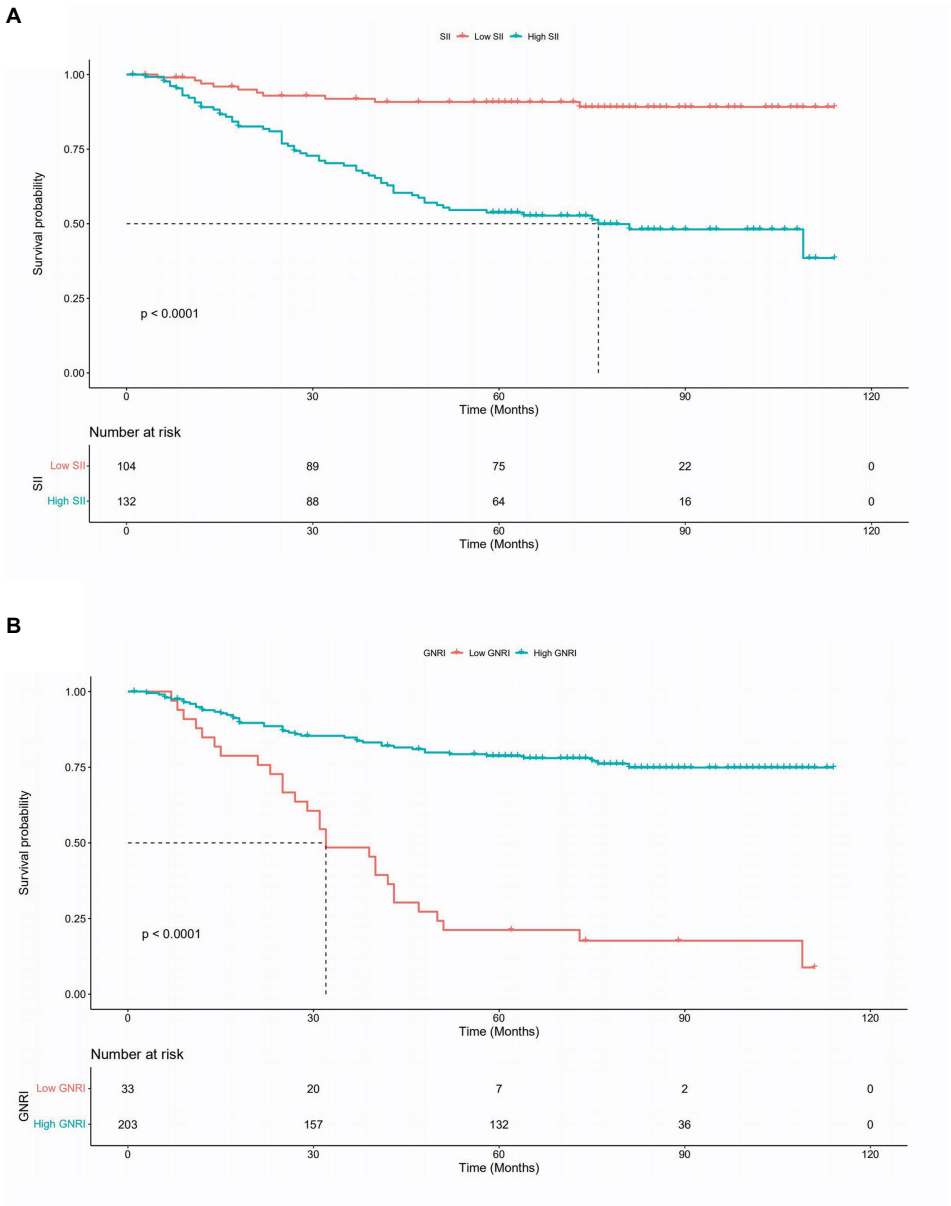

FIGURE 4
Kaplan–Meier survival curve for SII and GNRI in EOCRC. **(A)** SII **(B)** GNRI.

often associated with malnutrition and tumor progression (42). Various cytokines such as IL-6 and TNF can increase catabolism and reduce albumin synthesis in cancer patients. In our study, GNRI gradually decreased with increasing tumor stage, which may have been related to poor nutritional status and tumor progression. In addition, we found a significant negative correlation between GNRI and SII ($R = -0.3$, $p < 0.001$). With the gradual increase in SII, GNRI gradually decreased. Proinflammatory cytokines and growth factors can promote host catabolism and lead to muscle breakdown as part of the anti-tumor systemic inflammatory response (43). Low muscle strength can also lead to local inflammation of the muscle, which further leads to muscle breakdown and aggravates the systemic inflammatory response (44). Shlomit et al. (45) noted that in patients with solid tumors, a lower skeletal muscle index (SMI) at the time of cancer diagnosis was associated with a poorer survival rate and could be used as a prognostic indicator. George et al. (46) indicated that compared to patients with normal albumin levels, patients with reduced albumin levels had a significantly lower skeletal muscle index and visceral fat index at the L3 level. Thus, we speculate that GNRI reflects the muscle level of patients to a certain extent.

Identification of a high inflammatory state and low nutritional status in patients before surgery are of great clinical significance. Therefore, positive and timely therapeutic intervention can improve prognosis. Endurance- and resistance-type exercises can

TABLE 2 Univariate and multivariate analysis on the OS of SII.

Variables	OS (model 0)[a]		OS (model 1)[b]		OS (model 2)[c]	
	Crude HR (95%CI)	Crude *P*	Adjusted HR (95%CI)	Adjusted *P*	Adjusted HR (95%CI)	Adjusted *P*
As continuous (per SD)	1.07 (1.04–1.09)	0.000*	1.05 (1.03–1.10)	0.000*	1.08 (1.05–1.11)	0.000*
By SII cut-off						
≤637.6	/	/	/	/	/	/
>637.6	5.27 (2.91–9.54)	0.000*	4.22 (2.29–7.77)	0.000*	4.42 (2.36–8.27)	0.000*
By SII interquartile						
Q1 (~437.93)	/	/	/	/	/	/
Q2 (437.93–691.19)	3.74 (1.38–10.16)	0.009*	3.57 (1.31–9.75)	0.012*	4.09 (1.47–11.37)	0.006*
Q3 (691.19–890.71)	5.46 (2.08–14.33)	0.001*	3.93 (1.47–10.48)	0.006*	3.97 (1.45–10.86)	0.007*
Q4 (890.71~)	9.43 (3.69–24.09)	0.000*	7.19 (2.79–18.55)	0.000*	8.49 (3.22–22.36)	0.000*

SII, systemic immune inflammation index; OS, overall survival; HR, hazards ratio; CI, confidence interval;
[a]Model 0: Unadjusted.
[b]Model 1: Adjusted for age, gender, BMI and tumor stage.
[c]Model 2: Adjusted for age, gender, BMI, tumor stage, smoking, alcohol, tumor location, differentiated degree, nerve invasion, intravascular tumor emboli, preoperative therapy and postoperative therapy.
*$p \leq 0.05$.

TABLE 3 Univariate and multivariate analysis on the OS of GNRI.

Variables	OS (model 0)		OS (model 1)		OS (model 2)	
	Crude HR (95%CI)	Crude *P*	Adjusted HR (95%CI)	Adjusted *P*	Adjusted HR (95%CI)	Adjusted *P*
As continuous (per SD)	0.96 (0.95–0.97)	0.000*	0.97 (0.96–0.98)	0.000*	0.97 (0.96–0.98)	0.000*
By GNRI cut-off						
≤83.1	/	/	/	/	/	/
>83.1	0.23 (0.14–0.36)	0.000*	0.35 (0.21–0.58)	0.000*	0.33 (0.19–0.56)	0.000*
By GNRI interquartile						
Q1 (~91.50)	/	/	/	/	/	/
Q2 (91.50–100.37)	0.67 (0.41–1.13)	0.134*	0.85 (0.50–1.47)	0.582	0.70 (0.39–1.23)	0.219
Q3 (100.37–107.64)	0.23 (0.12–0.46)	0.000*	0.30 (0.15–0.61)	0.001*	0.29 (0.14–0.59)	0.001*
Q4 (107.64~)	0.21 (0.10–0.44)	0.000*	0.28 (0.13–0.62)	0.002*	0.29 (0.13–0.64)	0.002*

SII, GNRI, geriatric nutrition risk index; OS, overall survival; HR, hazards ratio; CI, confidence interval;
[a]Model 0: Unadjusted.
[b]Model 1: Adjusted for age, gender, BMI and tumor stage.
[c]Model 2: Adjusted for age, gender, BMI, tumor stage, smoking, alcohol, tumor location, differentiated degree, nerve invasion, intravascular tumor emboli, preoperative therapy and postoperative therapy.
*$p \leq 0.05$.

maintain skeletal muscle mass and function as well as energy balance (46). Recent studies have shown that to counteract catabolic effects, n-3 fatty acids can be used to reduce muscle loss (47), non-selective anti-inflammatory drugs can be used to alleviate the inflammatory response (48), and protein intake should be increased (49).

Because this was a retrospective study, certain limitations should be taken into consideration. First, due to missing data, we could not examine other markers of systemic inflammation such as lymphocyte-C reactive protein ratio and C-reactive protein/albumin ratio. Second, the study population was patients with early-onset colorectal cancer, which limits the generalizability of the results to other age groups and other tumor types. Third, the possibility of residual and unmeasured confounding could not be completely ruled out because of the retrospective nature of the study. Finally, this was a single-center retrospective study with small sample size and unbalanced distribution between GNRI groups may have a potential impact on the results. Therefore,

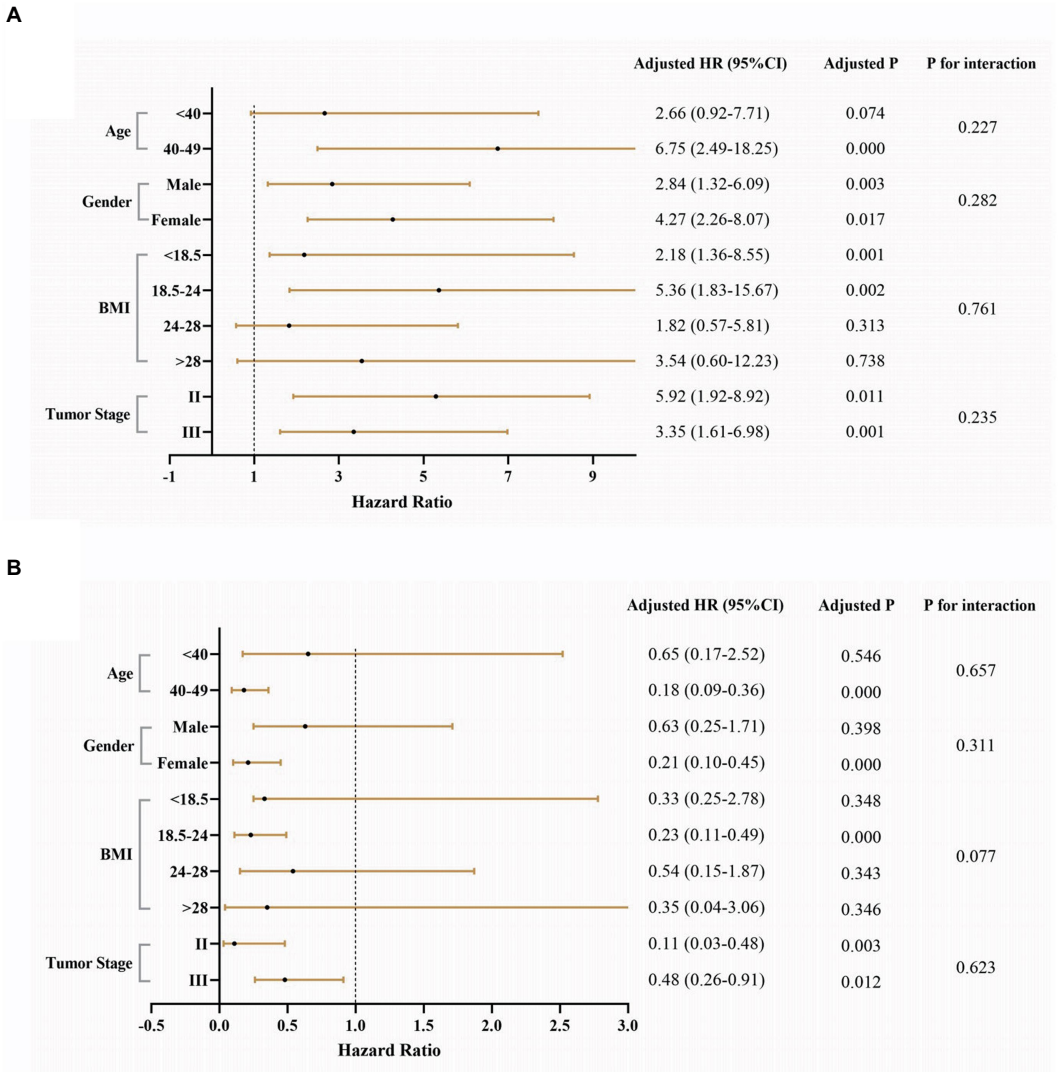

FIGURE 5
Stratification analysis of SII and GNRI in EOCRC. **(A)** High SII and low SII and **(B)** High GNRI and low GNRI. Adjusted for age, gender, BMI, tumor stage, smoking, alcohol, tumor location, differentiated degree, nerve invasion, intravascular tumor emboli, preoperative therapy, and postoperative therapy. Because the number of outcome events (deaths) in the stage I group was zero, we did not analyze this subgroup.

multi-center prospective studies are needed to confirm the effectiveness and prognostic ability of these nutritional and inflammatory markers.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SL and YG: conceptualization and supervision. SX, Y-XY, and W-JP: data curation, methodology, and software. SX and J-HZ: writing original draft. SL: review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1134300/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The optimal cut-off value of SII based on the survminer R software package.

SUPPLEMENTARY FIGURE S2
The optimal cut-off value of GNRI based on the survminer R software package.

SUPPLEMENTARY FIGURE S3
Pathway for patient recruitment and selection.

SUPPLEMENTARY FIGURE S4
Significant negative correlation between SII and GNRI.

SUPPLEMENTARY FIGURE S5
Survival prediction of SII in different subgroups.

SUPPLEMENTARY FIGURE S6
Survival prediction of GNRI in different subgroups.

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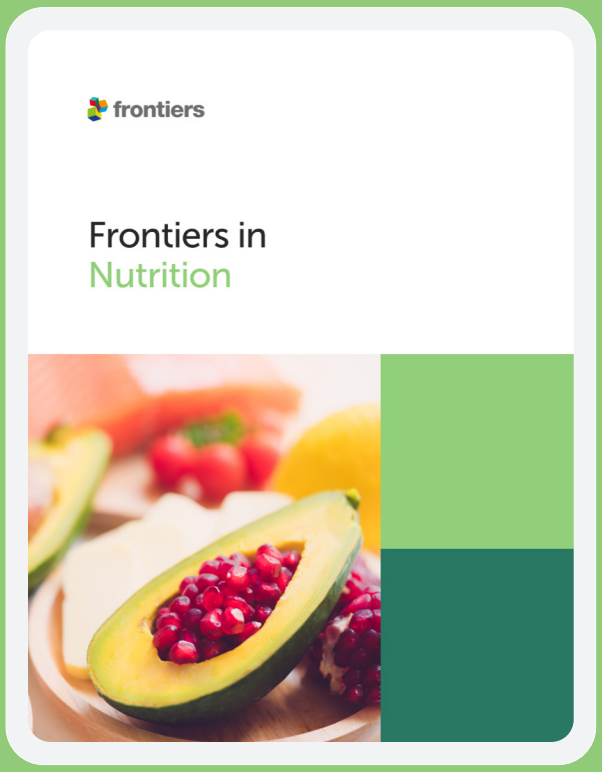

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