NUTRITIONAL ASSESSMENT TOOLS FOR IDENTIFICATION AND MONITORING OF MALNUTRITION IN PATIENTS WITH CHRONIC DISEASE

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EDITORIAL
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Editorial: Nutritional Assessment Tools for Identification and Monitoring of Malnutrition in Patients With Chronic Disease

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Keywords: sarcopenia, muscle strength, nutrition status assessment, malnutrition, chronic diseases

Editorial on the Research Topic

Nutritional Assessment Tools for Identification and Monitoring of Malnutrition in Patients With Chronic Disease

Chronic disease-related malnutrition (DRM) is a highly prevalent condition that is associated with prolonged hospital stays, higher morbidity and mortality, and increased economic burden. Its prevalence has been reported to be between 20 and 50% depending on the patient population and the criteria used for its diagnosis (1). Due to its clinical and economic consequences, nutritional screening of patients with chronic diseases should be conducted for the early detection and management of malnutrition. However, nutritional evaluation is not a routine practice in the clinical setting, and in the absence of standardized procedures, several operative diagnostic definitions for DRM have been proposed. The European Society for Clinical Nutrition and Metabolism, in its most recent guidelines on definitions and terminology of clinical nutrition, endorsed the following definition of malnutrition "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" (2). In addition, this organization recognized the existence of a specific type of DRM with inflammation, which is characterized by a catabolic condition with an inflammatory response, including anorexia and tissue breakdown elicited by an underlying disease (2). This is the type of malnutrition commonly seen in heart failure, chronic kidney disease, liver disease, arthritis, and cancer. Tools such as biomarkers, e.g., serum concentrations of visceral proteins, may be not valid in the context of DRM with inflammation and should not be used as indicators of a patient's nutritional status. Fluid retention is a factor related to DRM with inflammation that may be hindering valid assessment of changes in body cell mass and nutritional status, as documented in heart failure and chronic kidney disease (3, 4). Thus, identifying additional nutritional assessment tools for the proper identification of patients with nutritional abnormalities is urgently needed.

Sarcopenia is recognized as a nutrition-related condition that may be related to the aging process (primary sarcopenia); however, it may also result from pathogenic mechanisms (secondary sarcopenia) that are disease-related, activity-related, or nutrition-related (2). This condition is characterized by a progressive and generalized skeletal muscle disorder that is associated with increased risk of adverse outcomes including falls, fractures, physical disability, and mortality (5).

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This Research Topic addressed the current and novel nutritional assessment tools for identification and monitoring of malnutrition in patients with chronic disease. A total of 12 articles were published in this Research Topic covering different aspects of the above-mentioned topic. Sarcopenia was the topic of greatest interest; 5 out of 12 papers addressed this topic; including a systematic review aimed to explore the association between tongue strength and sarcopenia. This work showed that tongue strength is correlated with the subcomponents of sarcopenia, suggesting that sarcopenia is a systemic disease that may affect the skeletal muscles of the whole body, and that tongue pressure may be an indicator of subclinical dysphagia (Chen et al.). Also, data from Zhang, Zhang et al. highlighted the impact of sarcopenia and its muscle function and muscle composition components on clinical outcomes in an Asian population, while Mao et al. developed and evaluated the prognostic value of a novel index based on a combination of albumin-globulin score and sarcopenia in patients with renal cell carcinoma, showing a good performance of this index which reflects patient's nutritional and inflammatory status. Do et al. showed that phase angle assessed by the bioimpedance analysis technique is independently associated with muscle mass, strength, and sarcopenia in patients undergoing peritoneal dialysis, suggesting that phase angle can be used as a simple predictor of risk for sarcopenia in this patient population. Finally, Tejavath et al. reported results of a randomized clinical trial that demonstrated that long-term supplementation with branched-chain amino acids improved sarcopenia parameters and prognostic markers in elderly patients with advanced liver cirrhosis.

Four papers in this Research Topic provided evidence on the high prevalence of malnutrition and its prognostic value in diverse clinical conditions. Zhang, Qian et al. exhibited a high prevalence of malnutrition in elderly patients with cancer using three different scoring systems, ranging between 11.7 and 58.7%. Malnutrition was prevalent even in those who were overweight or obese as assessed by body mass index (BMI). Notably, malnutrition was associated with all-cause mortality regardless of the malnutrition index used, tumor types, and other risk factors, while deterioration of nutritional status was associated with deterioration in quality of life and immunotherapeutic response. Ding et al. also reported a high prevalence of patients at risk of malnutrition (77.76%) by using the NRS2002 screening tool and with mild/moderate malnutrition (10.09%) according to the Patient-Generated Subjective Global Assessment (PG-SGA) instrument among patients newly diagnosed with gastrointestinal stromal tumors. In patients undergoing coronary angiography (CAG) (Mai et al.), prevalence of malnutrition was also high and malnutrition-associated risk of mortality was higher in patients with left ventricular ejection fraction (LVEF) $\geq$40% than those with $<$40%, highlighting the need of giving greater attention to malnutrition in these patients. The impact of nutritional risk not only on health outcomes but hospital costs were also addressed by Liu et al. in a National Study of an Asian population.

Considering the potential utility of hypoalbuminemia as a therapeutic target for atrial fibrillation risk reduction, Wang et al. conducted a meta-analysis to assess the relationship between albumin and atrial fibrillation and the potential dose-response effect, demonstrating that a low serum albumin level was significantly associated with an increased risk of AF, paving the way for further studies aimed at exploring the effects of interventions to increase serum albumin levels for the prevention of AF. Nasab et al. also focused on the intervention aspects of malnutrition, particularly the differences between the feeding indications provided by a dietitian and a surgeon in patients undergoing gastrointestinal surgery who received parenteral nutrition. Results pointed out the relevance of incorporating a dietitian in the care of patients being arterially fed.

Finally, a valuable contribution to the field was provided by Marunowski et al., who proposed normative reference values for subcutaneous and visceral fat based on magnetic resonance imaging in a pediatric population, these are relevant data for the assessment of nutritional status in this Caucasian population from Poland.

Considering all mentioned contributions, it is evident that malnutrition is a topic of paramount interest in the health field. In the context of chronic disease, sarcopenia, muscle function (handgrip strength), muscle composition (low skeletal muscle mass index and low skeletal muscle radiodensity), and phase angle are all parameters that may be useful for nutritional assessment and monitoring since they are associated with clinically relevant outcomes and overall survival. Further research could be oriented toward developing population-specific normative values for muscle function and composition for a more accurate nutritional assessment in diverse patient populations.

AUTHOR CONTRIBUTIONS

EC-R wrote the introduction and central part with comments to 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.

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SYSTEMATIC REVIEW
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Assessment of Tongue Strength in Sarcopenia and Sarcopenic Dysphagia: A Systematic Review and Meta-Analysis

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Sarcopenic dysphagia is defined as difficulty in swallowing due to sarcopenia, which may be related to weakness of the tongue muscles. This meta-analysis aimed to explore the association between tongue strength and sarcopenia and to determine whether tongue strength measurement could be a specific indicator of sarcopenic dysphagia. We conducted a systematic search of electronic databases from their inception to February 2021 for clinical studies that investigated tongue strength in participants with and without sarcopenia. The primary outcome was the weighted mean difference (WMD) and standardized mean difference (SMD) of tongue pressure between the different groups. The secondary outcome was the correlation of tongue pressure with the subcomponents that defined sarcopenia. Ten studies that involved 1,513 participants were included in the meta-analysis. Compared with those without sarcopenia, patients with sarcopenia had significantly less tongue pressure, with a WMD of −4.353 kPa (95% CI, −7.257 to −1.450) and an SMD of −0.581 (95% CI, −0.715 to −0.446). There was no significant difference in tongue pressure between patients with sarcopenic dysphagia and those with non-sarcopenic dysphagia, with a WMD of −1.262 kPa (95% CI, −8.442 to 5.918) and an SMD of −0.187 (95% CI, −1.059 to 0.686). Significant positive associations were identified between tongue pressure and grip strength and between tongue pressure and gait speed, with correlation coefficients of 0.396 (95% CI, 0.191 to 0.567) and 0.269 (95% CI, 0.015 to 0.490), respectively. Reduced tongue strength is associated with sarcopenia but is not an exclusive marker for sarcopenic dysphagia. Tongue strength correlates with the values of subcomponents that define sarcopenia. In patients with

low performance of sarcopenia subcomponent, tongue pressure must be examined to diagnose subclinical dysphagia.

Protocol registration: This meta-analysis was registered on INPLASY (registration number INPLASY202120060).

Keywords: sarcopenia, dysphagia, tongue strength, frailty, tongue pressure

INTRODUCTION

Sarcopenia was first used by Rosenberg to describe an age-related decrease in muscle mass (1). According to the European Working Group on Sarcopenia in Older People (EWGSOP) (2) and the Asian Working Group for Sarcopenia (AWGS) (3) diagnostic criteria, sarcopenia is defined as low muscle mass, strength, and/or physical performance. The prevalence of sarcopenia has been reported to be between 1 and 29% in the community-dwelling population and between 14 and 33% in residents living in long-term care facilities (4). The association between sarcopenia and adverse health outcomes, such as mortality, incidence of falls, and longer hospitalization, has been reported in previous studies (5, 6). In addition, studies have shown that sarcopenia not only reduces the strength of limbs but also that of the oropharyngeal muscles, leading to swallowing impairment (7, 8).

Dysphagia is a term derived from Greek words, meaning worsening in eating (9) and is related to organic or neurological diseases, such as nasopharyngeal cancer, stroke, Parkinson's disease, and dementia (10). Sarcopenic dysphagia is characterized by sarcopenia of the entire body and swallowing-related muscles (11). The swallowing process can be divided into four phases: oral preparatory, oral, pharyngeal, and esophageal phases. The tongue plays a key role in bolus transport from the oral cavity to the pharynx. Tongue movements stimulate oropharyngeal receptors and trigger subsequent swallowing events (12). Abnormal tongue function is associated with oral and pharyngeal dysphagia (13). It has been reported that tongue strength is positively correlated with swallowing function (14). Aging-related fatty infiltration, amyloid deposition, and loss of tongue muscle fibers can lead to a decrease in tongue pressure (15). In addition, decreased tongue pressure during swallowing has been observed in patients with post-stroke dysphagia (16).

The diagnosis of sarcopenic dysphagia is important because sarcopenic dysphagia increases the risk of complications such as dehydration, malnutrition, and aspiration pneumonia (17). The prevalence of dysphagia in the sarcopenic population was reported to be 32% (18). Tongue strength measurement has been proposed as a diagnostic tool for sarcopenic dysphagia (19). The modified water swallowing test (MWST) has been widely used by medical practitioners to screen for dysphagia (20). However, it puts the examinees at risk of choking. The measurement of tongue strength is theoretically safer and more reliable than MWST. Since the measurement of tongue pressure is an objective method for assessing tongue strength, whether or not tongue pressure differs in the sarcopenic population is a clinically important issue. Therefore, the purpose of the meta-analysis was two-fold: (1) to explore the association between tongue strength and sarcopenia and (2) to determine whether tongue strength measurement could be a specific indicator for sarcopenic dysphagia.

Abbreviations: WMD, Weighted mean difference; SMD, standardized mean difference; MWST, modified water swallowing test; EWGSOP, the European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia.

METHODS

Protocol Registration

The study was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) program (21). The meta-analysis was prospectively registered on Inplasy.com (INPLASY202120060).

Studies Search and Selection

PubMed (US National Library of Medicine) and Embase (Wolters Kluwer Ovid) were searched for cross-sectional, case-control, and cohort studies that investigated tongue strength in the sarcopenia population from their inception to February 2021. Key search terms included: "sarcopenia," "frailty," "dysphagia," "swallowing disorder," "tongue pressure," "tongue strength" (**Appendix 1**). There was no restriction on language during the literature search. Furthermore, relevant narratives and systemic reviews were manually retrieved for potentially eligible articles.

Inclusion and Exclusion Criteria

Studies were included if they: (1) investigated human subjects over the age of 18 years; (2) provided measurements for tongue pressure; (3) provided how sarcopenia was evaluated and (4) evaluated swallowing performance. The study types were divided into cross-sectional studies, cohort studies, case-control studies, and clinical trials.

The following studies were excluded: (1) case reports, case series, and research protocols; (2) studies that did not measure tongue pressure and sarcopenia components; (3) studies that validated technologies or devices for tongue strength assessment; and (4) studies that lacked a control group with normal muscle volume and function.

Quality Assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of each study (22). It evaluates eight aspects of each retrieved study: representativeness of sarcopenic patients, selection of control, ascertain of tongue pressure measurement, outcome of interest not present at start, comparability of

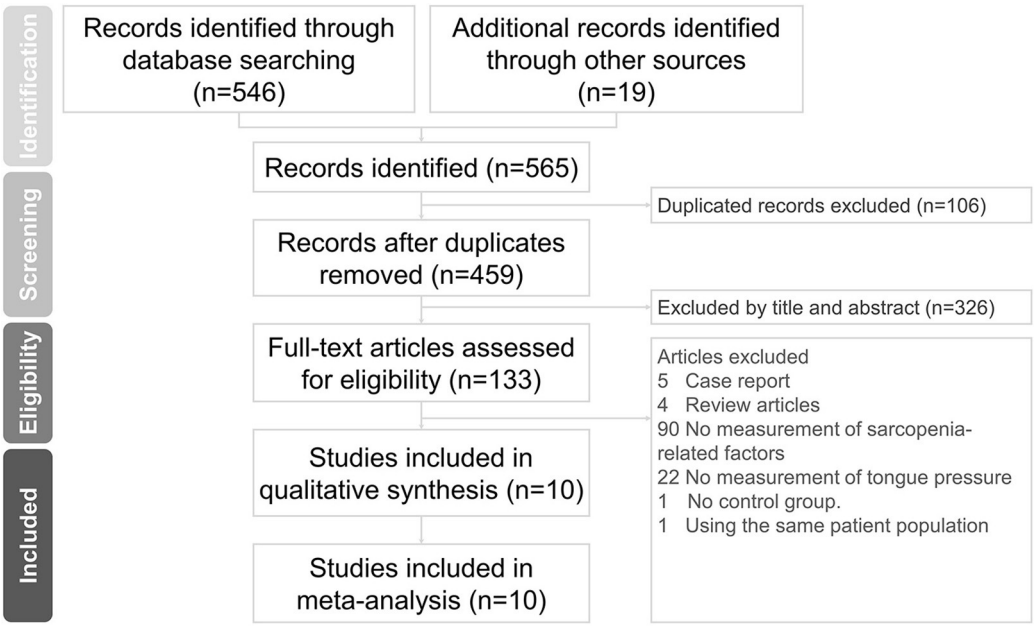

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study.

cohorts, assessment of outcome, enough follow-up period, and adequacy of follow-up. The quality assessment was conducted by both reviewers individually, while the outcomes of the evaluation were decided based on a consensus or by the corresponding author.

Data Extraction

Two authors (K.C.C and K.V.C) independently screened the titles and abstracts to determine whether the articles met the scope of the present meta-analysis. The full texts of the pertinent articles were retrieved for further data extraction. The author, publication year, study design, diagnostic criteria for sarcopenia, number of included patients, population characteristics, sex ratio, and data collection period were extracted from all included studies. If some data were missing in the published articles, the corresponding authors of the original studies were contacted for the required information. Questions arising from data abstraction were resolved through discussions or by the corresponding author.

Statistical Analysis

The primary outcome included the weighted mean difference (WMD) and standardized mean difference (SMD) between the groups. The SMD was calculated as the difference in the mean tongue pressure divided by the pooled standard deviation (23). The WMD provided the absolute between-group difference in tongue pressure in kPa, whereas the SMD facilitated the awareness of the magnitude of the effect regarding tongue strength discrepancy for the two target populations. An SMD of 0.2, 0.5, and 0.8, is considered a small, moderate, and large effect size, respectively (24). The secondary outcome was the correlation of tongue pressure with the subcomponents of sarcopenia. The correlation coefficients were analyzed using the Hedges-Olkin method based on the Fisher Z transformation of the variables (25). We also analyzed the association between sarcopenia and low tongue pressure using the risk ratio (26).

The random effect model was used for pooling the data, considering the variations in the study designs and enrolled participants. The between-group heterogeneity was evaluated using the Cochrane's Q and I^2 statistics. An $I^2 > 50\%$ was considered to indicate significant heterogeneity (27). Publication bias was determined by visual inspection of the funnel plots and the p-value of the Egger's test (28). All statistical analyses were conducted using Comprehensive Meta-analysis Software v 3 (Biostat, Englewood, NJ), and a $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Literature Search

The initial literature search identified 565 articles. After excluding 106 duplicate articles and 326 non-relevant articles by screening their titles and abstracts, 133 studies were eligible for subsequent evaluation. Five case reports, four review articles, 90 studies that did not measure sarcopenia-related factors, 22 studies that did not assess tongue pressure, one study without a control group, and one study (29) involving the same patient cohort as another study were excluded (**Figure 1**). Finally, a total of ten articles were included in the meta-analysis (8, 18, 30–37). These articles

TABLE 1 | Characteristics of the included study.

References	Study design	Patient characteristic	Outcome measurement	*N* Sarcopenia	*N* non-sarcopenic	Age	Sex ratio M/F	Data collection period	Swallowing evaluation tool	Country
Shimizu et al. (37)	Cross-sectional	Admissions for orthopedic conditions, aged ≥ 65 years, no history of cerebrovascular or neuromuscular disease, without an implanted pacemaker	TP, MNA-SF, BMI, FIM	105	92	81.3 ± 7.6	39/158	November 2018 to September 2019.	FOIS MASA	Japan
Chen et al. (35)	Cross-sectional	Elderly sarcopenic patients without dysphagia, age ≥ 65 years, living independently, fully cooperative, eat orally	TP, Submental ultrasonography,100-mL WST	47	47	75.1 ± 5.8	26/68	NA	EAT-10	Taiwan
Kobuchi et al. (36)	Cross-sectional	Patients living in nursing homes or university hospitals	TP, BMI, oral examination, BI, MNA-SF, cross-sectional area of the geniohyoid muscle, oral diadochokinesis	18	36	78.8 ± 7.1	16/38	NA	EAT-10	Japan
Sakai et al. (34)	Cross-sectional	age > 65 years, post-acute phase of illness hospitalized for rehabilitation, MMSE ≥ 21, presence of all upper and lower central incisors	TP, 100-mL WST, swallowing time, swallowing speed, lip force, MMSE, CCI, MNA-SF	86	159	84.0 (79–88)*	79/166	April 2015 to October 2016	FOIS	Japan
Wakabayashi et al. (18)	Prospective cohort	age > 65 years, dysphagia, referred for speech therapy	TP, BI, GNRI, BMI, total energy intake, C-reactive protein	35	73	76 ± 7	72/36	August 2016 to March 2018	FILS	Japan
Kaji et al. (33)	Cross-sectional	Type 2 diabetes, age ≥ 60 years, tolerate standing position	TP, smoking, exercise, hemoglobin A1c	17	127	71.4 ± 6.7	82/62	April 2017 to October 2017	Nil	Japan
Suzuki et al. (32)	Cross-sectional	Community-dwelling older women, age ≥65 years, walk independently, absence of dysphagia	TP, oral diadochokinesis, BMI	29	216	81.0 (75.0–85.0)*	NA	NA	EAT-10	Japan
Ogawa et al. (8)	Cross-sectional	Acute care hospitals or convalescent rehabilitation hospitals or long-term care hospitals or nursing homes, age> 65 years, able to answer a questionnaire	TP, thickness and area of the tongue and geniohyoid muscles, MNA-SF, BMI	36	19	82.1 ± 7.4	31/24	October 2016 to April 2017	FILS	Japan
Machida et al. (30)	Cross-sectional	Community-dwelling older adults, living independently	TP, MNA-SF, jaw-opening force, BI	68	129	78.5 ± 6.7(M) 77.8 ± 6.2(F)	97/100	NA	EAT-10	Japan
Sakai et al. (31)	Cross-sectional	age ≥65 years, post-acute phase of illness, living independently, no history of dysphagia, MMSE ≥ 21, presence of upper and lower central incisors	TP, BI, MNA-SF, BMI, serum albumin levels, CONUT, modified WST	134	40	84 (80–89)*	64/110	October 2014 to December 2015	FOIS EAT-10	Japan

*WST, water swallowing test; EAT, Eating assessment tool; TP, tongue pressure; BI, Barthel Index; MNA-SF, Mini Nutritional Assessment-Short Form; MMSE, Mini Mental State Examination; CCI, Charlson Comorbidity Index; FILS, Food Intake Level Scales; GNRI, Geriatric Nutritional Risk Index; BMI, body mass index; FOIS, functional oral intake scale; EAT-10, 10-item Eating Assessment Tool; CONUT, controlling nutritional status; FIM, Functional Independence Measure; MASA, Mann Assessment of Swallowing Ability; NA, not available; *Interquartile range (IQR).*

TABLE 2 | Diagnostic tools and criteria of sarcopenia in the included studies.

References	Muscle strength	Muscle volume	Muscle function	Diagnostic algorithm
	Cut-off points			
Shimizu et al. (37)	Jamar digital handgrip gauge (MG-4800; CHARDER Electronic, Taichung, Taiwan)	BIA	NA	AWGS: low HGS + low SMI
	<28 kg for male, <18 kg for female	②	NA	
Chen et al. (35)	Handheld dynamometer	DEXA/BIA	5-m walk test	AWGS: low HGS + low SMI ± low gait speed
	①	③/②	④	
Kobuchi et al. (36)	Handgrip dynamometer (Takei Scientific Instruments Co., Ltd).	BIA	5-m walk test in a 9 m path	AWGS: low SMI + low HGS or low gait speed
	①	③	④	
Sakai et al. (34)	Digital grip strength dynamometer	CC	NA	AWGS: low HGS + low CC
	①	<34 cm for male; <33 cm for female	NA	
Wakabayashi et al. (18)	NA	CC	NA	AWGS: low HGS + low CC ± low gait speed
	①	<30 cm for male; <29 cm for female	④	
Kaji et al. (33)	Handgrip dynamometer (Smedley; Takei Scientific Instruments, Niigata, Japan)	BIA	NA	AWGS: low HGS + low SMI
	①	②	NA	
Suzuki et al. (32)	Handgrip dynamometer (TTM, Tokyo, Japan)	BIA	5-m walk test	AWGS: low HGS + low SMI ± low gait speed
	①	②	④	
Ogawa et al. (8)	Grip strength	CC	NA	AWGS: low HGS + low CC ± low gait speed
	①	<34 cm for male; <33 cm for female	④	
Machida et al. (30)	Handgrip dynamometer (TTM, Tokyo, Japan)	BIA	4-m walk test in 8 m path	AWGS:(low SMI + low HGS) or (low SMI + low gait speed)
	Not clear mentioned	Not clear mentioned	Not clear mentioned	
Sakai et al. (31)	Digital grip strength dynamometer	CC	NA	EWGSOP: low HGS + low CC
	<30 kg for male, <20 kg for female	<34 cm for male; <33 cm for female	NA	

DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CC, calf circumference; AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; HGS, hand grip strength, SMI, skeletal muscle mass index.

Cuff off points:

①, Hand grip strength: male: <26 kg, female: <18 kg.

②, Skeletal muscle mass index: male: <7.0 kg/m^2, female:<5.7 kg/m^2.

③, Skeletal muscle mass index: male: <7.0 kg/m^2, female:<5.4 kg/m^2.

④, Gait speed <0.8 m/s.

comprised of nine cross-sectional studies (8, 30–37) and one cohort study (18). Data on the number of sarcopenic and non-sarcopenic groups were missing in one study and were retrieved by contacting the corresponding author of the article (36). The details of the included studies are presented in **Table 1**.

Study Characteristics

The ten studies involved 1,513 participants, with the mean (or median) ages ranging from 71.4 to 84.0 years. Three studies recruited community-dwelling older adults (30, 32, 35), three recruited hospitalized older people (18, 31, 34), one recruited elderly patients with type 2 diabetes (33), one recruited older patients admitted for orthopedic conditions (37) and two recruited older adults who required rehabilitation (8, 33). Regarding the diagnostic algorithm for sarcopenia, one study employed the EWGSOP guidelines (31) and nine employed the AWGS criteria (8, 18, 30, 32–37). The diagnostic tools and criteria for sarcopenia in the included studies are shown in **Table 2**. The tools used for the evaluation of swallowing function are summarized in **Table 1**. They include the 10-item Eating Assessment Tool, Functional Oral Intake Scale, Food Intake Level Scale, and MWST and Mann Assessment of Swallowing Ability.

TABLE 3 | Quality assessment for the included studies by using the newcastle-ottawa scale.

	Representative of sarcopenia patients	Selection of control	Ascertain of sarcopenia measurement	Outcome of interest not present at start	Comparability of cohorts	Assessment of outcome	Enough follow-up period	Adequacy of follow up	Total point
Shimizu et al. (37)	★	★	★	★	★★	★			7
Chen et al. (35)	★	★	★	★	★★	★	-	-	7
Kobuchi et al. (36)	★	★	★	★	★★	★	-	-	7
Sakai et al. (34)	★	★	★	★	★★	★	-	-	7
Wakabayashi et al. (18)	★	★	★	★	★★	★	★	★	9
Kaji et al. (33)	★	★	★	★	★★	★	-	-	7
Suzuki et al. (32)	★	-	★	★	★★	★	-	-	6
Ogawa et al. (8)	★	★	★	★	★★	★	-	-	7
Machida et al. (30)	★	★	★	★	★★	★	-	-	7
Sakai et al. (31)	★	★	★	★	★★	★	-	-	7

★, *numbers of points earned in each cell.*

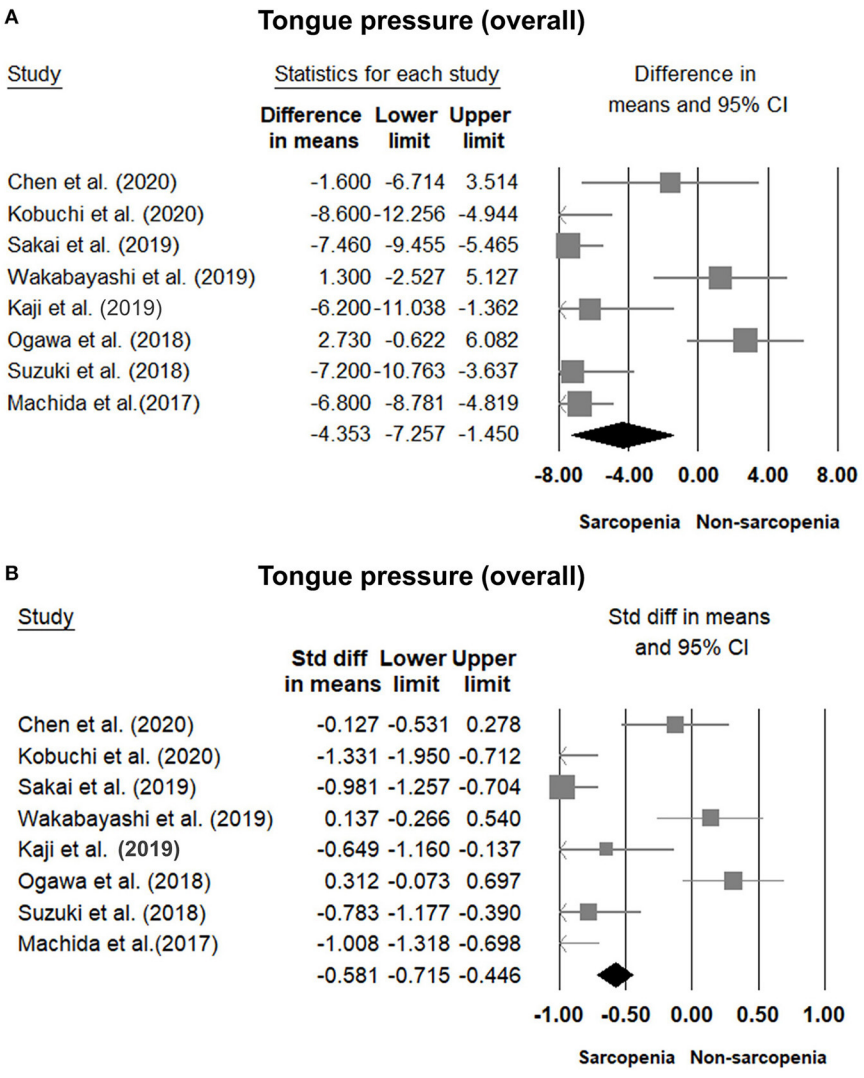

FIGURE 2 | Forest plot of the tongue pressure in the overall participants quantified by the weighted mean difference **(A)** and standardized mean differences **(B)**.

Quality Assessment of the Included Studies

The results of the quality assessment are presented in **Table 3**. The domains for which most studies failed were "enough follow-up period" and "adequacy of follow-up." This is because the cross-sectional design was employed in the majority of the enrolled articles and the studies did not involve a longitudinal follow-up. The results of the quality assessment are shown in **Table 3**.

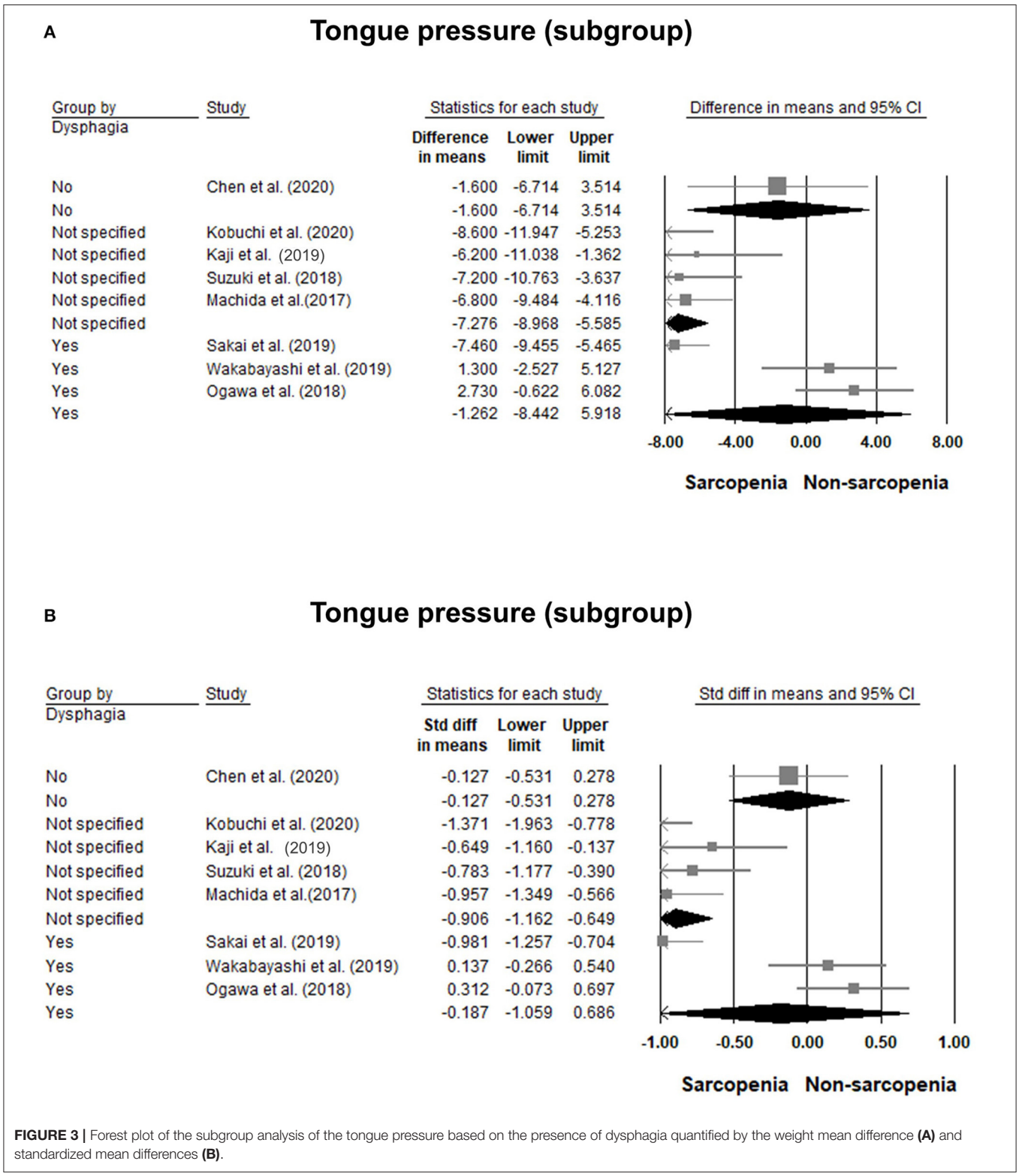

FIGURE 3 | Forest plot of the subgroup analysis of the tongue pressure based on the presence of dysphagia quantified by the weight mean difference **(A)** and standardized mean differences **(B)**.

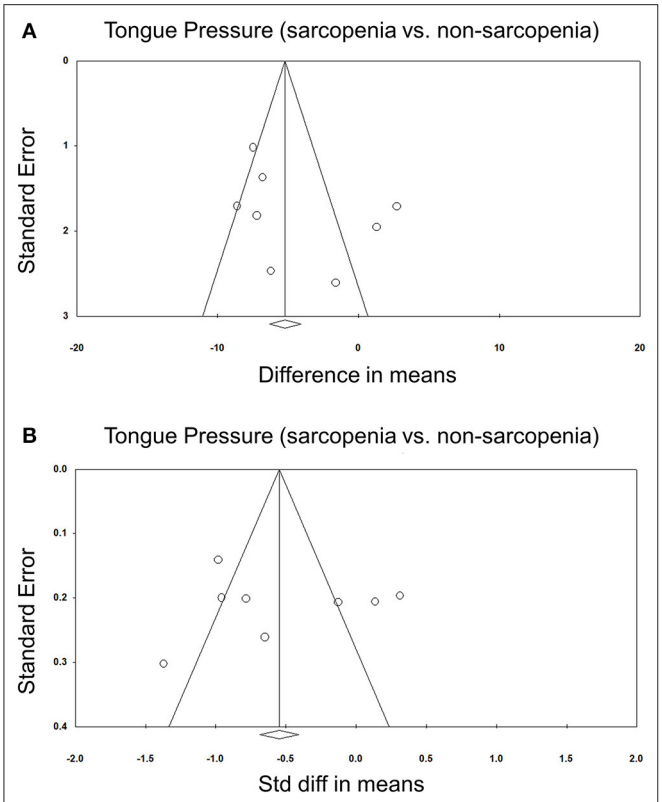

FIGURE 4 | Funnel plot of the weighted mean difference **(A)** and standardized mean differences **(B)** of the tongue pressure between the sarcopenic and non-sarcopenic groups among the included studies. Std diff, standardized difference.

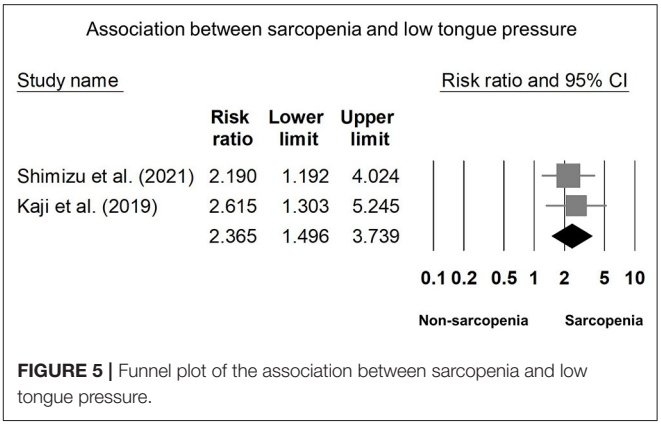

FIGURE 5 | Funnel plot of the association between sarcopenia and low tongue pressure.

Comparisons of Tongue Pressure Between the Sarcopenic and Non-sarcopenic Group

Eight of our included studies (8, 18, 30, 32–36) compared tongue pressure. Compared with the non-sarcopenic group, patients with sarcopenia had significantly lower tongue pressure, with a WMD of −4.353 kPa (95% CI, −7.257 to −1.450; I^2 = 84.9%) and an SMD of −0.581 (95% CI, −0.715 to −0.446; I^2 = 88.2%) (**Figure 2**). Subgroup analysis was performed based on the presence of dysphagia. In studies that recruited patients with dysphagia (8, 18, 34), there was no significant difference in the tongue pressure between the non-sarcopenic and sarcopenic groups, with a WMD of −1.262 kPa (95% CI, −8.442 to 5.918; I^2 = 94.1%) and an SMD of −0.187 (95% CI, −1.059 to 0.686; I^2 = 94.5%). In studies that enrolled patients without specifying whether or not they had dysphagia (30, 32, 33, 36), the sarcopenic group still had significantly lower tongue pressure than the non-sarcopenic group, with a WMD of −7.112 kPa (95% CI, −8.601 to −5.623; I^2 < 0.01%) and an SMD of −0.921 (95% CI, −1.152 to −0.690; I^2 = 15.3%). Only one study included participants without clinical dysphagia (35). The patients in the aforementioned study had a WMD of −1.600 kPa (95% CI, −6.714 to 3.514) and an SMD of −0.127 (95% CI, −0.531 to 0.278) (**Figure 3**). Visual inspection of the funnel plots and *p*-values following the Egger's test revealed no significant publication bias (**Figure 4**). The association between sarcopenia and low tongue pressure was available in two (33, 37) of our included studies. The threshold for defining low tongue pressure was 20 kPa in the one conducted by Shimizu et al. (37) and 21.6 kPa in the one conducted by Kaji et al. (33). The pooled analysis indicated that sarcopenia was associated with low tongue pressure, with a risk ratio of 2.365 (95% CI, 1.496 to 3.739; I^2 < 0.001) (**Figure 5**).

Comparisons of Tongue Pressure Between Men and Women

Comparisons of tongue pressure between male and female participants were available in five studies (8, 30, 31, 33, 34). No significant gender differences (men vs. women) were identified. The WMD was 0.759 kPa (95% CI, −1.518 to 3.037; I^2 = 70.0%) and the SMD was 0.088 (95% CI, −0.183 to 0.358; I^2 = 70.2%) (**Figure 6**). No significant publication bias was detected based on visual inspection of the funnel plots and *p*-values following Egger's test (**Figure 7**).

Correlation of Tongue Pressure With Subcomponents of Sarcopenia

The correlation coefficient between tongue pressure and grip strength was available in three studies (29, 31, 36), with a pooled value of 0.396 (95% CI, 0.191 to 0.567). The results of the correlation analysis between tongue pressure and grip strength in the study conducted by Machida et al. (30) was derived from that reported by another study (29), since both studies involved the same population of patients. Two of the included studies (29, 36) reported a correlation coefficient between tongue pressure and gait speed, with a pooled value of 0.269 (95% CI, 0.015 to 0.490) (**Figure 8**). Likewise, the correlation analysis of tongue pressure and gait speed in the study conducted by Machida et al. (30) was available from another study (29), since both studies involved the same population of patients. The aforementioned analyses indicated a significant positive correlation between tongue pressure, grip strength, and gait speed.

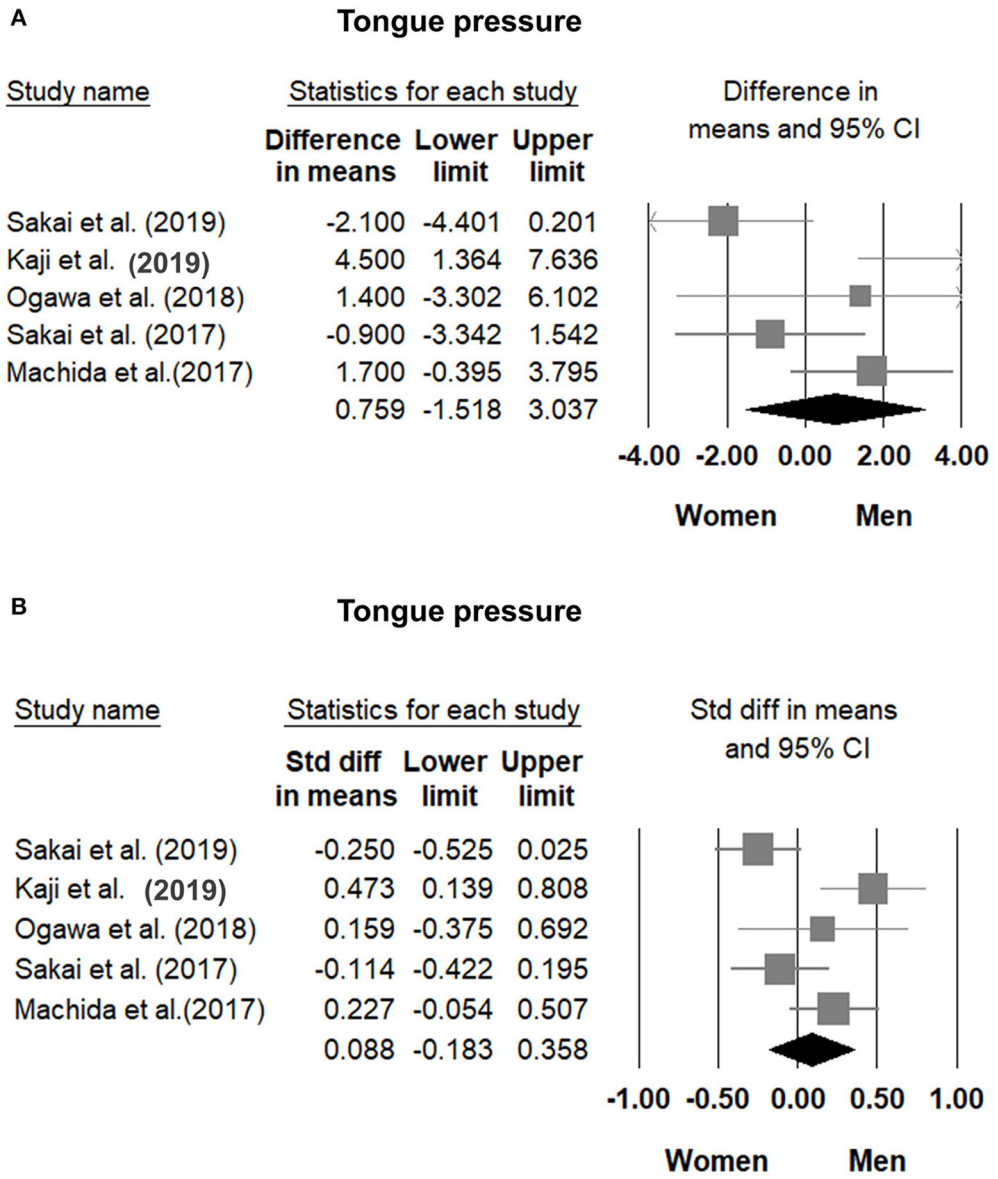

FIGURE 6 | Forest plot of the weighted mean difference **(A)** and standardized mean differences **(B)** of tongue pressure between men and women. Std diff, standardized difference.

DISCUSSION

The main finding of this study was that elderly patients with sarcopenia had significantly lower tongue pressure than those without sarcopenia. The subgroup analysis further revealed that there was no significant difference in tongue pressure between patients with sarcopenic dysphagia and those with non-sarcopenic dysphagia. No significant gender differences in tongue pressure were identified in our target population. In addition, a positive association existed between tongue pressure and subcomponents of sarcopenia, including grip strength and gait speed.

In our analysis, patients with sarcopenia had significantly lower tongue pressure, with an SMD of −0.581, indicating a moderate between-group difference. Although the mechanism is not clearly understood, a possible reason is that the generalized decline of muscle mass and strength in the sarcopenic population also affects swallowing-related muscles, such as the tongue, infra-hyoid, supra-hyoid, and pharyngeal muscles. Type II muscle fibers are affected by malnutrition, a potential cause of sarcopenia, more easily than type I muscle fibers (38). Therefore, the swallowing muscles are vulnerable to the effects of insufficient nutrition due to its higher type II fiber content (39). These factors may lead to decreased tongue strength,

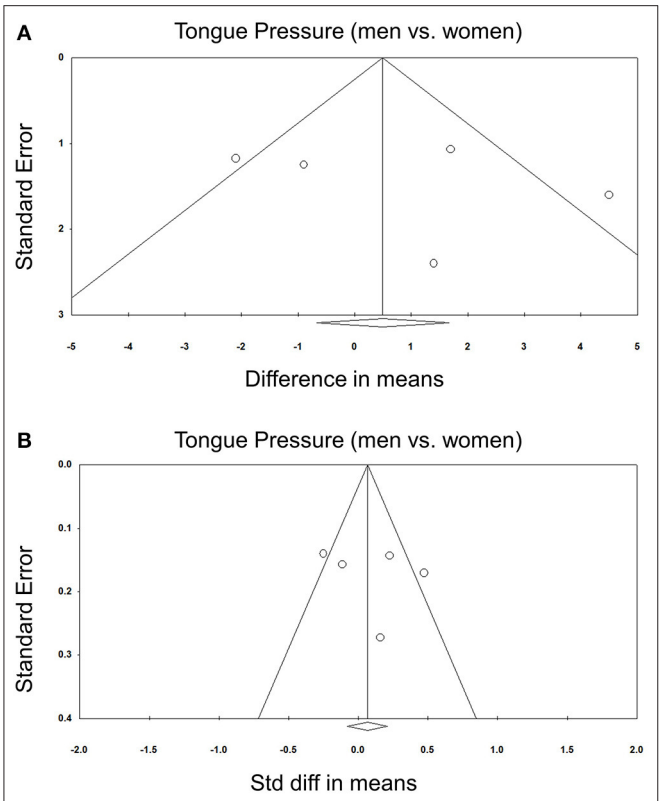

FIGURE 7 | Funnel plot of the weighted mean difference **(A)** and standardized mean differences **(B)** of the tongue pressure between men and women among the included studies. Std diff, standardized difference.

reduced range of tongue motion, weak contractility of pharyngeal muscle, impaired endurance of swallowing-related muscles, and an increased risk of dysphagia in patients with sarcopenia (13). In addition, a previous study found that tongue-pressure resistance training could improve tongue and supra-hyoid muscle function simultaneously and might be helpful for the prevention of sarcopenic dysphagia (40). Hence, our findings are consistent with existing evidence showing reduced tongue strength in the sarcopenic population.

However, there was no significant difference in tongue pressure between patients with and without sarcopenic dysphagia. We speculated that patients with dysphagia had decreased oral intake, which potentiated disuse atrophy of the tongue muscles regardless of pre-existing sarcopenia. Furthermore, neurological diseases such as stroke (41) and Parkinsonism (42) lead to uncoordinated posterior tongue movement and prolonged tongue elevation (43), which interfere with tongue pressure measurement and subsequent underestimation of tongue strength. Therefore, our findings showed that reduced tongue pressure was not an exclusive indicator of sarcopenic dysphagia.

No gender differences in tongue pressure were identified in our study population. A previous study also revealed no significant gender differences in isometric and peak swallowing pressure measured by intraoral pressure sensors in 20 healthy participants (44). In contrast, some studies have revealed that men have greater maximum tongue pressures than women (45, 46). There were two factors that led to the absence of gender differences in our meta-analysis. First, our study population consisted mainly of older adults, whose tongue strength had already decreased with age. Second, the analysis involved patients with sarcopenia whose tongue strength had also been reduced, based on our analysis. Therefore, since tongue strength declined in our study participants, the gender difference in tongue strength was trivial.

The included studies revealed a positive correlation between tongue pressure, physical performance, and grip strength. Grip strength and physical performance are considered objective measurements of muscle function, a subcomponent of sarcopenia (2, 3). Our findings indicate that sarcopenia is a systemic disease that affects skeletal muscles in the whole body. The decline in tongue strength was shown to be proportional to the impact on the skeletal muscles of the limbs. A previous study reported that nutritional support and rehabilitation exercises to restore physical function could improve sarcopenic dysphagia (47). Therefore, in patients with low sarcopenia subcomponent values or performance, tongue pressure must be examined to detect subclinical dysphagia.

There are several limitations that must be acknowledged. First, the present meta-analysis included a relatively low number of studies. An updated meta-analysis may be needed in the future to include more prospective trials to confirm the association of tongue strength with sarcopenia and sarcopenic dysphagia. Second, all enrolled studies evaluated Asian populations. The generalizability of our findings to other ethnicities requires further validation. Third, nine studies used the AWGS criteria to diagnose sarcopenia (8, 18, 30, 32–37), and one study used the EWGSOP criteria (31). The difference in the diagnostic criteria for sarcopenia led to between-study heterogeneity. Fourth, videofluoroscopic evaluation of swallowing was not performed in the studies that recruited patients with dysphagia. Therefore, it was difficult to investigate which phase of swallowing was impaired in these patients and how it was related to tongue pressure. Fifth, the majority of the included studies employed a cross-sectional design. Therefore, the causal relationship between sarcopenia and reduced tongue strength was not elucidated in our meta-analysis.

CONCLUSION

Based on our meta-analysis, reduced tongue strength is associated with sarcopenia; however, it is not an exclusive marker for sarcopenia. In addition, tongue strength is correlated with the subcomponents of sarcopenia, implying that sarcopenia is a systemic disease that affects the skeletal muscles of the whole body. Therefore, in patients with low sarcopenia subcomponent values or performance, tongue pressure must be examined to detect subclinical dysphagia.

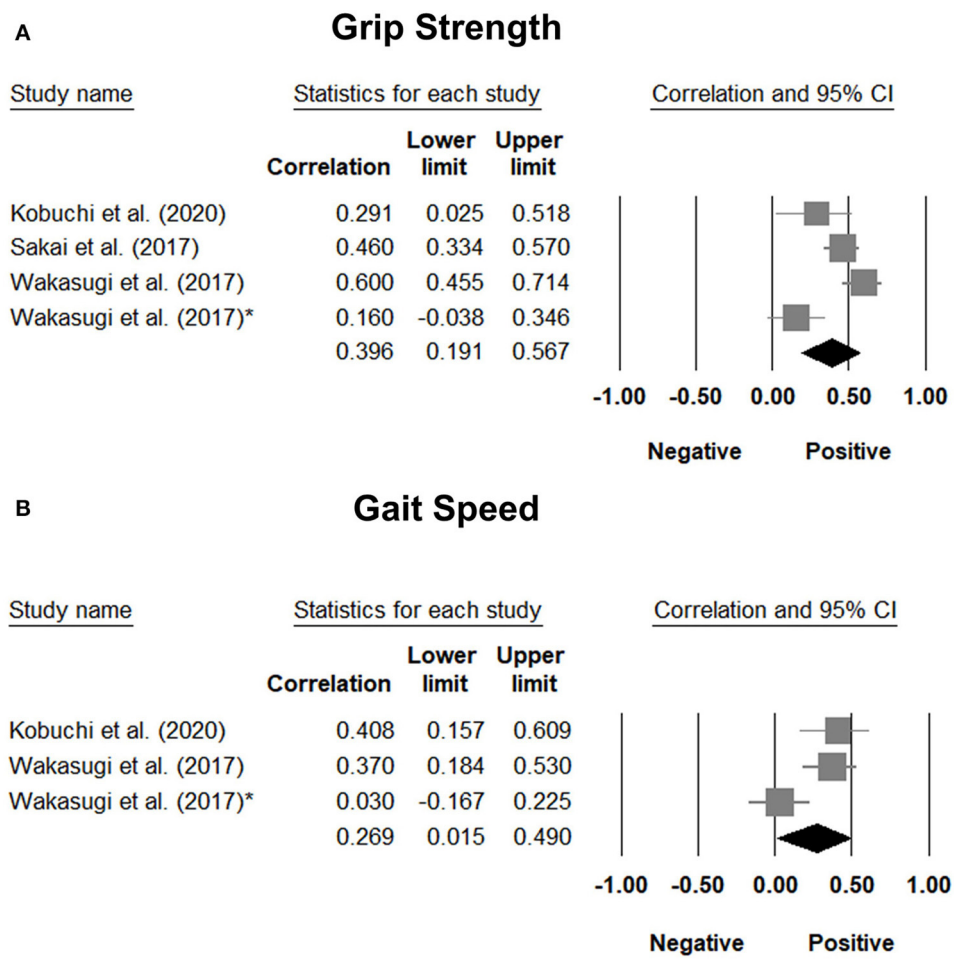

FIGURE 8 | Forest plot of the correlation analysis between tongue pressure and grip strength **(A)** and between tongue pressure and gait speed **(B)**. In the study performed by Wakasugi et al., the correlation analysis was conducted based on different genders. The one without the asterisk is the male subgroup, where as the one with the asterisk is the female subgroup.

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/s.

AUTHOR CONTRIBUTIONS

K-VC, K-CC, and T-ML conceived and designed the study, recruited the study subjects, and planned and performed the statistical analysis. W-TW, T-GW, D-SH, K-VC, and K-CC contributed to study supervision and critical revision of the manuscript. All authors have read and approved the final manuscript.

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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.2021.684840/full#supplementary-material

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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.

frontiers in Nutrition

SYSTEMATIC REVIEW
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Relationship Between Serum Albumin and Risk of Atrial Fibrillation: A Dose-Response Meta-Analysis

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Background: The dose–response association between serum albumin and atrial fibrillation is not well known. This study aims to assess the relationship between albumin and atrial fibrillation and the potential dose–response effect.

Methods: Studies reported that the serum albumin and AF were identified by searching the EMBASE, PubMed, and Cochrane Library databases. The potential dose–response effect was performed by using a stage robust error meta-regression.

Results: Nine studies were included with a total of 32,130 individuals. Patients with high albumin level were associated with a decreased risk of atrial fibrillation compared with patients with low serum albumin (OR[odds ratio]: 0.62, 95% CI [0.44, 0.89]; $I^2 = 76\%$; $P = 0.009$). In the dose–response analysis, for each 10 g/L increase in serum albumin level, the risk of atrial fibrillation decreased by 36% (95% CI: 0.51–0.81, $I^2 = 87\%$, $P < 0.001$). Furthermore, a significant negative linear relationship between serum albumin and the risk of atrial fibrillation ($P_{nonlinearity} = 0.33$) was found.

Conclusion: Our dose–response meta-analysis suggests that low serum albumin level is associated with an increased risk of atrial fibrillation. Further studies are needed to explore the effect of induction of elevated serum albumin levels on the prevention of atrial fibrillation.

Keywords: atrial fibrillation, dose-response, risk factor, nutrition, albumin

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the clinical setting, with a substantially increased morbidity, mortality and bring tremendous economic. Although multiple risk factors, including cardiovascular and noncardiovascular risk factors, have been identified (1), the potential modifiable risk factors are yet to be explored.

Albumin is a predominant protein in human plasma (2). Hypoalbuminemia, usually defined as <35 g/L, is a significant indicator of malnutrition, inflammation, or cachexia and has been recognized as a robust biomarker for various noncardiovascular and cardiovascular diseases (3, 4) in the general population or patients with coexisting diverse comorbidities (5, 6). Several studies and our previous study have reported the malnutrition status and the risk of AF

(7–11) as an indicator of malnutrition, however, the serum albumin and associated risk of AF is inconclusive. Moreover, the dose–response relationship of albumin and AF is still unclear. Given this background, we aim to perform a meta-analysis to assess the relationship between albumin and AF and the potential dose–response effect.

METHODS

We performed this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Supplementary Table 1**) (12).

Search Strategy

Database search, selection, data extraction, and statistical analysis were independently conducted by two authors (YL and XL). For all relevant studies, three databases (PubMed, Embase, and the Cochrane Library) were searched up to May 27, 2021. No language restrictions were applied. The following search terms were used for all of the databases: ("albumin" OR "hypoalbuminemia" OR "serum albumin") AND ("atrial fibrillation" OR "auricular fibrillation"). Report data on adults ≥18 years of age that helped assess the association between serum albumin and risk of AF were included. In addition, the conference abstracts and bibliographies of related works of literature were scanned. The detail of the search strategy was listed in **Supplementary Table 2**.

Selection Criteria and Study Selection

Following studies that satisfied the inclusion criteria were selected: (1) studies that reported the serum albumin level and risk of AF; (2) those designed as randomized controlled trials or observational studies; (3) those that made available a quantitative measure of serum albumin level and the corresponding estimate effect and 95% CI in each albumin category for the dose–response analysis. Accordingly, reviews, meta-analyses, congress abstracts, practice guidelines, patents, cases, editorials, replies, or comments studies were excluded. Any inconsistency was resolved through discussions (YL and XL) until consensus was reached.

Data Collection and Quality Assessment

Data of each study were extracted based on prespecified inclusion criteria, including the first author, publication year, geographical location, study type, participants (sex, age, and sample size), adjustments for confounders, categories of serum albumin, and adjusted odds ratios (ORs) with its 95% confidence intervals (CIs) for each serum albumin category. We included the articles with the longest follow-up or the largest numbers of participants for multiple publications and reports by using the same data. The Newcastle–Ottawa quality scale (NOS) or the Joanna Briggs Institute (JBI) critical appraisal checklist (cross-sectional study) was applied for quality assessment (13). The JBI critical appraisal checklist (https://jbi.global/critical-appraisal-tools) composed eight items, which score each study for the following items: participant selection, exposure definition, statistical analysis, and outcome data. Studies with a NOS or JBI of ≥6 stars were considered moderate- to high-quality articles (14).

Statistical Analysis

Summary ORs and 95% CIs for a 10-g/L increment in serum albumin were pooled by using a random-effects model after considering the potential heterogeneity. The risk ratio is treated as equal to ORs (15). We calculated the study-specific slopes (linear trends) and 95% CIs from the natural logs of the reported ORs and CIs across categories of serum albumin by using the method described by Greenland and Longnecker (16). Nonlinear dose–response models were fitted by using the robust error meta-regression method (17, 18) that required at least two quantitative serum albumin level ORs with variance estimates. We estimated the midpoint of each category by averaging the lower and upper boundaries of that category if the median or mean serum albumin was not provided and reported in ranges (19). If the highest or lowest category was open-ended, we assumed that the open-ended interval length was the same as the adjacent interval (15). To assess the heterogeneity of ORs across studies, the I^2 (95% CI) statistic was calculated with the following interpretation: low heterogeneity, defined as $I^2 < 50\%$; moderate heterogeneity, defined as I^2 50%−75%; and high heterogeneity, defined as $I^2 > 75\%$ (15). Moreover, subgroup analyses were stratified by variables of interest, such as mean age, study population, study design, and adjustments. All analyses were performed using Stata 16.0 (Stata Corp LP, College Station, TX, USA) and Review Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014; Nordic Cochrane Center Copenhagen, Denmark). A $P < 0.05$ was considered statistically significant.

RESULTS

Literature Search

The selection process of the study is shown in **Figure 1**. We identified 421 articles through an initial database search. After removing the duplicated articles, 300 reports remained. We further excluded 276 articles by quickly screening the titles and abstracts and reviewed 24 articles in more detail. Of the 24 records, 15 were excluded (e.g., reviews and duplicated population) after the full-text review. The details of the reasons to exclude them are described in **Supplementary Table 3**. Finally, 9 (7–11, 20–23) eligible studies (10 cohorts) with 32,130 individuals were included.

Study Characteristics and Study Quality

The baseline characteristics of each study were listed in **Table 1**. Overall, six studies reposted a positive association between the serum albumin and risk of AF, while three cohorts showed a null association. They were published from 2009 to 2020, with three from Europe, four from Asia, and two from United States. The mean age of participants ranged from 52 to 67 years old. AF diagnosis was based on the electrocardiogram among all works of literature. Four studies were prospective cohort, four were retrospective cohort, and one was a cross-sectional study.

Abbreviations: AF, Atrial fibrillation; CI, Confidence interval; OR, Odds ratio; NOS, Newcastle-Ottawa Scale score.

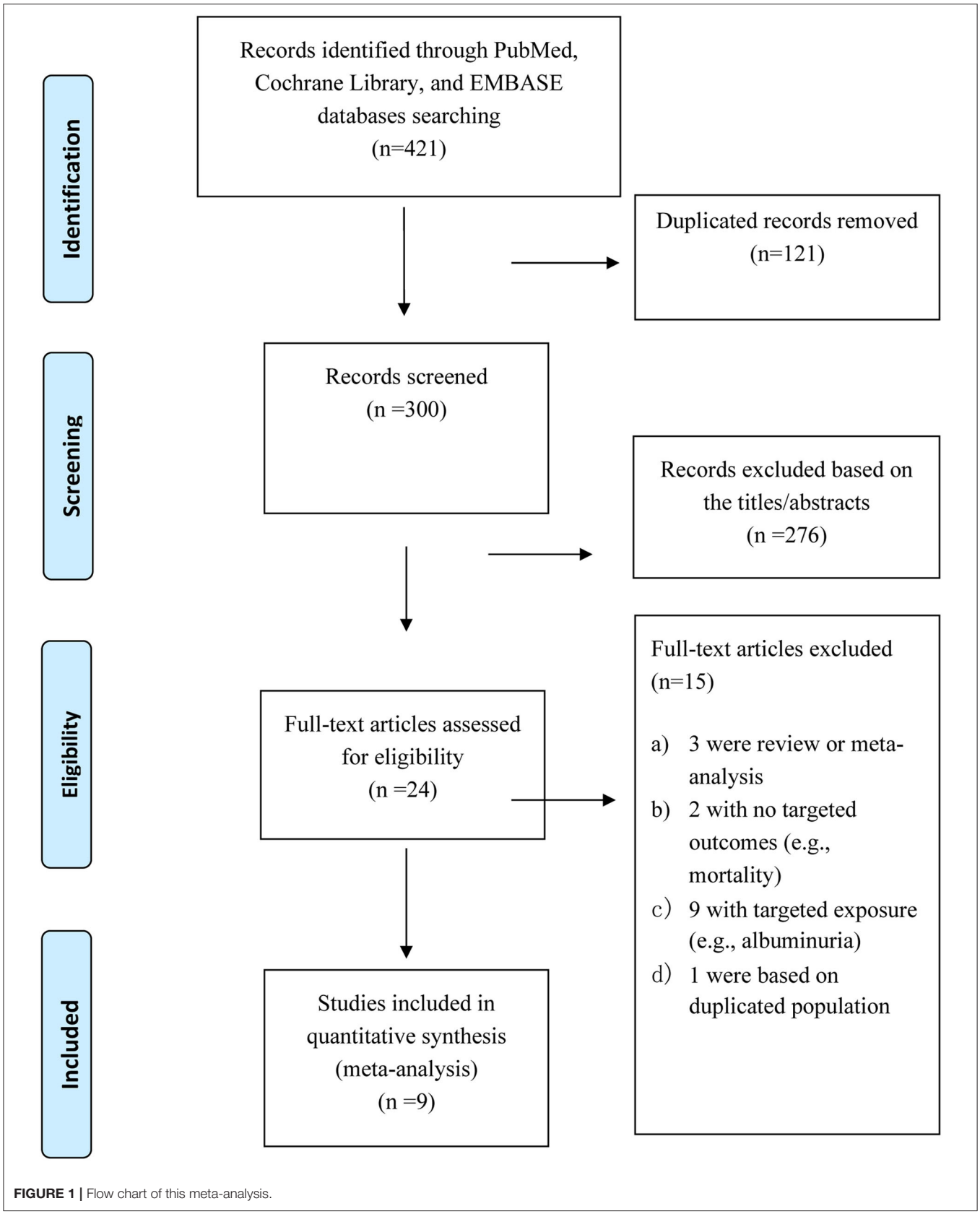

FIGURE 1 | Flow chart of this meta-analysis.

TABLE 1 | Baseline characteristic of included studies in the association between serum albumin and atrial fibrillation.

Author, year, Country	Sample size	Data source	Population	Design	Mean age (years), Male (%)	AF diagnosis/ Follow-up	Albumin level reported	OR	95%CI	Adjustments	Study quality*
Beek (10), Netherlands	97	Maxima Medical Center	Hospitalized in ICU	Prospective cohort	67, 53	ECG/na	Per 1 g/l increase	0.86	0.77–0.97	Age, previous AF, prior use of anti-arrhythmic drug, severe sepsis, potassium, magnesium, calcium	6
Acar (11), Turkey	183	Karimnagar's State Hospital	Hemodialysis patients	Retrospective cohort	52, 48	ECG/na	Per 1 g/dl decrease	1.25	0.22–7.14	Age, right atrium diameter, left atrium diameter, Left ventricle mass index, E/E, pulmonary artery pressure, valvular calcification, duration of hemodialysis	6
Tanaka (9), Japan	1,524	Aichi Cohort Study	Chronic kidney disease	Prospective cohort	67, 68.5	ECG/na	Per 1 mg/dl increase	0.56	0.32–0.96	Age, sex, CAD, CRP	8
Liu (21), China	3,489	People's Hospital of Peking University	Inpatient	Retrospective cohort	62, 55.8	ECG/na	<35 g/L ≥35 g/L	2.02 Ref	1.43–2.84	Age, sex, heart failure, cardiomyopathy, rheumatic heart disease, hyperthyroidism, SUA	6
Mukamal (22), Danish	8,870	Copenhagen City Heart Study	Free of cardiovascular disease	Prospective cohort	55, na	ICD/7.5 years	women <461 g/L 461–478 478–496 >496 Men <468 468–486 486–506 >506	Ref 2.04 1.10 2.14 Ref 1.41 1.41 1.98	 1.10–3.80 0.57–2.13 1.15–3.96 0.64–3.09 0.64–3.09 0.94–4.17	Age, smoking, BMI, and sex, height, physical activity, education, family history of CVD, co-habitation, FEV1, systolic blood pressure, and history of diabetes	7
Liao (8), US	15,792	Atherosclerosis Risk in Communities	General Population	Prospective cohort	53, 54	ECG/25 years	Per 1 g/dl increase ≤ 3.7 g/dl 3.7–3.9 3.9–4.0 > 4.0	0.67 Ref 0.87 0.83 0.80	0.56–0.80 0.78–0.97 0.72–0.95 0.71–0.91	Age, race, gender, BMI, waist-hip ratio, heart rate, smoking, drinking, education, income, heart failure, CAD, DM, hypertension, Na, K, creatinine, non-albumin protein, uric acid, HDL-c, LDL-c, triglycerides, total cholesterol, glucose, antihypertension medicine, stain, aspirin, anticoagulation medicine, white blood cell	8

(Continued)

TABLE 1 | Continued

Author, year, Country	Sample size	Data source	Population	Design	Mean age (years), Male (%)	AF diagnosis/ Follow-up	Albumin level reported	OR	95%CI	Adjustments	Study quality*
Karabacak (7), Turkey	830	University of Health Sciences	CABG	Retrospective cohort	63, 75	ECG/na	Per 1 g/dl increase	0.438	0.25-0.86	Age, CRP, CRP/albumin ratio	6
Mwalitsa (23), Italy	335	Liver Unit of the University Hospital of Messina"	Cirrhosis	Retrospective cohort	65, 65	ECG	Per 1 g/dl increase	0.41	0.05-0.33	None	5
Ananthapanyasut (20), US		Advocate Christ Medical Center	Non-dialysis Patients with Chronic Kidney Disease	Cross sectional	65, 52	ECG	Per 1 g/dl increase	0.48	0.39-0.58	None	6

AF, atrial fibrillation; HF, heart failure; CRP, C-reactive protein; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ECG, Electrocardiography; ICD, International classification of diseases; SUA, serum uric acid; CVD, cardiovascular diseases; ICU, intensive care unit; FEV1, Forced Expiratory Volume in the first second; OR, odd ratio; CABG, coronary artery bypass graft; na, not available.

** Study quality was assessed by Newcastle-Ottawa Scale (cohort and case-control study) or Joanna Briggs Institute Critical Appraisal Checklist (cross-sectional study).*

Two studies were general population based and others included hospitalized patients.

Association Between Serum Albumin Level and Risk of AF

Three studies (8, 21, 22) with 28,651 reported category analyses between serum albumin and risk of AF. As shown in **Figure 2A**, high serum albumin level was associated with decreased risk of AF (OR: 0.62, 95% CI [0.44, 0.89]; $I^2 = 76\%$; $P = 0.009$) (highest vs. lowest) with significant heterogeneity.

Eight studies (7–11, 20–23) (nine cohorts) with 28,641 participants were included in the exposure–effect analysis. A 10-g/L increment in serum albumin decreased the risk of AF by 36% (95% CI: 0.51–0.81, $I^2 = 87\%$, $P < 0.001$) (**Figure 2B**). Heterogeneity was not significant when excluding Liao et al. (8) while the summary OR was still significant (OR: 0.47, 95% CI: 0.40–0.56, $I^2 = 0\%$, $P < 0.001$). In the nonlinear model, there was a significant negative linear association between serum albumin and risk AF ($P_{\text{linearity}} = 0.33$) (**Figure 3**).

Subgroup Analysis and Sensitive Analysis

We conducted subgroup analyses stratified by age, region, confounding factors, and potential intermediate factors. As shown in **Table 2**, among hospitalized patients, there was a significant inverse association between albumin and AF (OR: 0.48, 95% CI: 0.40–0.56, $I^2 = 0\%$, $P < 0.001$), however, it was not significant in the group of general population (OR: 0.85, 95% CI: 0.71–1.01, $I^2 = 56\%$, $P = 0.07$). The association between serum albumin and the risk of AF persisted in other subgroups, including age, regions, publication years, sample size or adjusted for age, sex, cardiovascular diseases, and C-reactive protein (**Table 2**). The results were stable by omitting one study at once (**Figure 4**), excluding the studies with crude analysis and those that reported AF postoperation or cross-sectional study (**Table 2**). According to the guidelines, meta-regression and publication bias were not conducted after considering the limited numbers of included studies ($N < 10$).

DISCUSSION

This study showed a significant negative linear association between serum albumin and risk of AF, where 10-g/L serum albumin decreased the risk of AF by 36%. The results were stable in most of the subgroup and sensitive analysis, suggesting the robustness of our findings. To the best of our knowledge, this is the first meta-analysis to assess serum albumin and AF association.

Atrial fibrillation occurs in fewer than 1% of persons aged 60–65 years; however, it could reach 8–10% of those older than 80 years (1). A firm link between hypoalbuminemia and the incidence of many cardiovascular diseases was established, such as ischemic diseases, stroke, and diabetes (24–27). Moreover, these associations were independent of conventional risk factors, such as body mass index, liver function, and inflammation. Consistently, in the present study, an inverse association between serum albumin level and the risk of AF was found. There Several

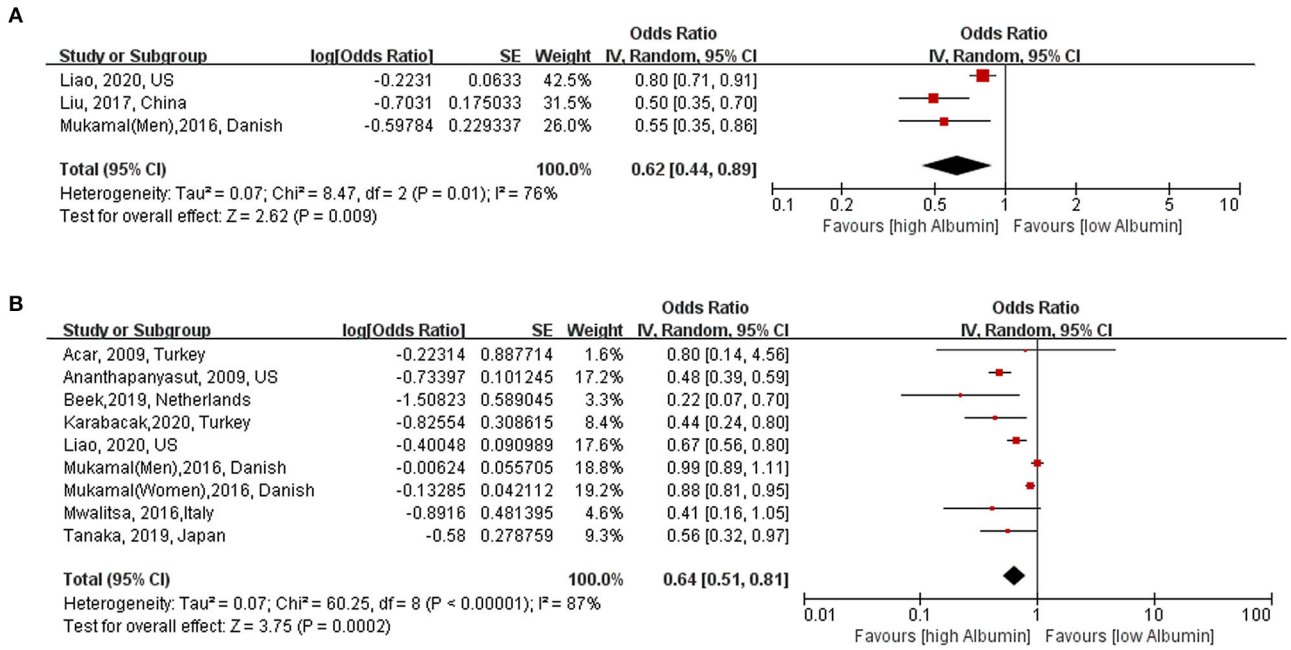

FIGURE 2 | Association between serum albumin level and risk of atrial fibrillation. **(A)** Category analysis (highest vs. lowest) **(B)**: Continuous analysis (per 10 g/L increase). AF, atrial fibrillation; OR, odd risk.

potential mechanisms have been prosposed. Inflammation has been identified as one of the important mechanisms contributing to the incidence of AF (28). Serum albumin exerts a powerful anti-inflammatory function in physiological conditions (29). Several studies have reported that albumin has a positive association with various circulating levels of inflammatory factors, such as tumor necrosis factor-alpha and C-reactive protein (29). Furthermore, albumin represents a very abundant and important circulating antioxidant (e.g., free radicals and reactive oxygen species) (29, 30). Free-radical-associated damage is an important factor in the pathological processes of AF (31). Experimental studies showed that elevated reactive oxygen species might modify ion channel activity to increase AF susceptibility by increasing sarcoplasmic reticulum Ca^{2+} release *via* enhanced ryanodine receptor activity, shortening of the atrial action potential duration, and producing delayed afterdepolarizations (31, 32).

Our subgroup results showed a significant association between albumin and AF in the general population; however, it was not significant in patients with comorbidities (hospitalized patients). There might be several potential expansions. First, most of the studies based on hospitalized patients with comorbidities were retrospective and might introduce a larger bias. The residue confounding might enlarge the association of albumin and AF. Second, recent studies also have shown that albumin was a potential connection with cardiovascular diseases and diabetes. Therefore, we propose that the association between low serum albumin and AF may be amplified in patients with comorbidities or at high risk of developing comorbidities. However, considering the limited sample size, the role of serum albumin in patients with comorbidities or at high comorbidities risk needs to be further investigated. Further studies with prospective design and a larger sample size are required.

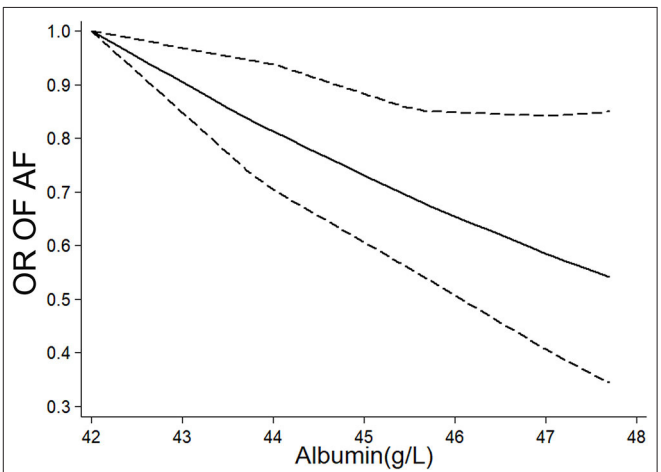

FIGURE 3 | Nonlinear exposure–effect analysis between serum albumin level and risk of atrial fibrillation, the solid and dashed lines represent the estimated odd risk and the 95% confidence interval, respectively. AF, atrial fibrillation; OR, odd risk.

Previous findings showed discrepant effects of albumin among men and women. Among women of the Copenhagen City Heart Study, a protective effect was noted with a significant linear association. All categories of albumin showed no benefit of AF

TABLE 2 | Subgroup analysis and sensitive analysis of serum albumin and risk of atrial fibrillation.

Items		Number of cohorts	OR	I^2%	*P*
					Within subgroup
Subgroup analysis					
Mean age	<65 years	4	0.48 [0.40, 0.57]	58	<0.001
	≥65 years	5	0.81 [0.67, 0.97]	34	0.004
Region	Northern America	4	0.74 [0.57, 0.95]	94	0.02
	Europe	2	0.32 [0.15, 0.67]	0	0.002
	Asia	3	0.51 [0.35, 0.76]	92	0.002
Study quality	≤ 6 scores	3	0.47 [0.39, 0.57]	26	0.007
	6 high scores	6	0.78 [0.65, 0.94]	73	<0.001
Publication yeas	2009–2017	4	0.55 [0.39, 0.76]	38	0.003
	2017–2021	5	0.73 [0.54, 0.97]	64	0.01
Sample size	< 1,000	6	0.40 [0.26, 0.64]	14	<0.001
	≥ 1,000	4	0.72 [0.56, 0.91]	92	0.007
Population	General population	3	0.85 [0.71, 1.01]	56	0.07
	Hospitalized patients	6	0.48 [0.40, 0.56]	0	<0.001
Adjusted for age	Yes	7	0.75 [0.61, 0.91]	78	0.003
	No	2	0.48 [0.39, 0.58]	21	<0.001
Study design	Prospective cohort	5	0.87 [0.82, 0.93]	82	<0.001
	Retrospective cohort	3	0.45 [0.28, 0.74]	0	0.001
	Others	1	0.48 [0.39, 0.59]	-	<0.001
Adjusted for sex	Yes	4	0.82 [0.69, 0.98]	82	0.03
	No	5	0.47 [0.39, 0.56]	0	<0.001
Adjusted for CAD	Yes	4	0.82 [0.69, 0.98]	82	0.03
	No	5	0.47 [0.39, 0.56]	0	<0.001
Adjusted for CRP	Yes	4	0.82 [0.69, 0.98]	82	0.03
	No	5	0.47 [0.39, 0.56]	0	<0.001
Sensitivity analysis					
	Excluding crude analysis	7	0.75 [0.61, 0.91]	78	0.003
	Excluding POAF	8	0.67 [0.53, 0.85]	88	0.001
	Excluding cross-sectional studies	8	0.73 [0.60, 0.88]	76	0.001

CRP, C-reactive protein; CVD, cardiovascular diseases; POAF, post-operation atrial fibrillation; OR, odd ratio.

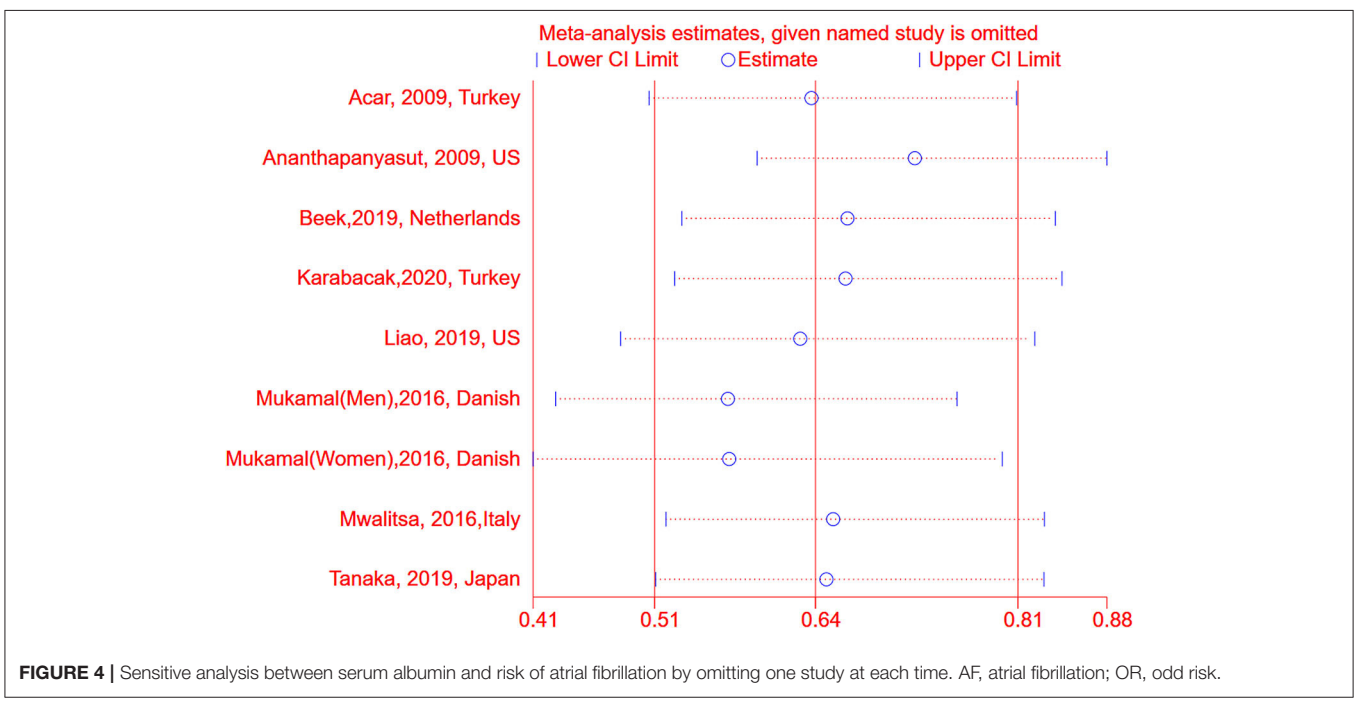

FIGURE 4 | Sensitive analysis between serum albumin and risk of atrial fibrillation by omitting one study at each time. AF, atrial fibrillation; OR, odd risk.

compared with lowest ablumin level among men. In contrast, findings from the Atherosclerosis Risk in Communities cohort showed a significant protective effect of albumin, regardless of sex. The contrasting results regarding sex might derive from different baseline characteristics, such as region, race, age, and follow-up time. For example, the incidence of AF in the Copenhagen City Heart Study and Atherosclerosis Risk in Communities cohort differ significantly, with 3.2% (286/8864, 7.5 years follow-up) for the Copenhagen City Heart Study and 17.6% (2259/12833, 25.1 years follow-up) for the Atherosclerosis Risk in Communities cohort. The protective effect of albumin among men might appear as the prolonged time of follow-up in the Copenhagen City Heart Study. Therefore, it is still unclear whether there is a gender difference in the association between albumin and AF and should be further studied.

CLINICAL IMPLICATIONS

The measurement of serum albumin is simple, cheap, and routinely available. Given the potential link between low serum albumin level and AF, albumin supplement (such as albumin infusion or protein supplementation) for patients with hypoalbuminemia might be a therapeutic target for reducing the risk of AF. Decreased serum albumin levels imply an undernourished state, which usually leads to poor clinical outcomes. For example, AF post cardiac operation was one of the most common complications, low albumin levels have been reported to be a significant predictor for AF after coronary artery bypass graft surgery (7). However, currently, there is limited evidence to assess the effect of albumin on reducing the risk of AF. Further studies are needed to identify the role of albumin in the prevention of AF.

STRENGTHS AND LIMITATION

This is the first meta-analysis that reported the association between albumin and AF risk and the robustness of the findings in multiple subgroup analyses. However, several limitations also should be recognized. First, this is an observation-based study, which cannot deduce the causal relationship. Low serum albumin level is an indicator of undernutrition status. Serum albumin might be an intermediate factor in the association between undernutrition status and risk of AF. Unmeasured and insufficiently measured variables could have resulted in residual confounding. Second, as we know, sex is an independent risk factor for AF. A sex difference might exist in the association between albumin and the risk of AF (22). However, we could also not perform a subgroup analysis stratified by sex due to data restriction. Third, the number of included studies is limited. Further larger and well-designed studies were needed to confirm our conclusion. Fourth, the protocol of this study was not prospectively registered, however, no similar protocols of this topic were registered in the International prospective register of systematic reviews (PROSPERO) database (https://www.crd.york.ac.uk/prospero/). Finally, there was substantial heterogeneity in the primary analysis, which may derive from the baseline characteristics of patients. However, there was no evidence of heterogeneity when Liao et al. was excluded, with results remaining positive.

CONCLUSION

Our dose–response suggested low serum albumin level is significantly associated with an increased risk of AF. Further studies are needed to explore the effect of induction of elevated serum albumin levels on the prevention of AF.

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/s.

AUTHOR CONTRIBUTIONS

XZ and JT were responsible for the entire project and revised the draft. XL and YW performed the systematic literature review and drafted the first version of the manuscript. All authors took part in the interpretation of the results and prepared the final version of the manuscript.

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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.2021.728353/full#supplementary-material

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Association of Malnutrition, Left Ventricular Ejection Fraction Category, and Mortality in Patients Undergoing Coronary Angiography: A Cohort With 45,826 Patients

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Background: The regulatory effect of the left ventricular ejection fraction (LVEF) categories on the association of malnutrition and all-cause mortality in patients undergoing coronary angiography (CAG) have not been adequately addressed.

Methods: Forty-five thousand eight hundred and twenty-six patients consecutively enrolled in the Cardiorenal ImprovemeNt (CIN) study (ClinicalTrials.gov NCT04407936) from January 2008 to July 2018 who underwent coronary angiography (CAG). The Controlling Nutritional Status (CONUT) score was applied to 45,826 CAG patients. The hazard ratios of mortality across combined LVEF and/or malnutrition categories were estimated by Cox regression models. Variables adjusted for in the Cox regression models included: age, gender, hypertension (HT), DM, PCI, coronary artery disease (CAD), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TRIG), chronic kidney disease (CKD), statins, atrial fibrillation (AF), anemia, and stroke. Population attributable risk (PAR) was estimated for eight groups stratified by nutritional status and LVEF categories.

Results: In our study, 42,181(92%) of patients were LVEF $\geq$ 40%, of whom, 41.55 and 9.34% were in mild and moderate or severe malnutrition status, respectively, while 46.53 and 22.28% in mild and moderate or severe malnutritional status among patients with LVEF $<$ 40%. During a median follow-up time of 4.5 years (percentile 2.8–7.1), 5,350 (11.7%) patients died. After fully adjustment, there is no difference of mortality on malnutrition in LVEF $<$ 40% group (mild, moderate and severe vs. normal, HR (95%CI): [1.00 (0.83–0.98)], [1.20 (0.95–1.51)], [1.41 (0.87–2.29)], respectively, p for trend =0.068), but malnutrition was related to markedly increased risk of mortality in LVEF $\geq$ 40% group (mild, moderate, and severe vs. normal, HR (95%CI): [1.21 (1.12–1.31)],

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[1.56 (1.40–1.74)], and [2.20(1.67–2.90)], respectively, p for trend <0.001, and p for interaction <0.001). Patients with LVEF ≥ 40% had a higher malnutrition-associated risk of mortality and a higher PAR than those with LVEF < 40%.

Conclusions: Malnutrition is common in CAG patients and it has a greater effect on all-cause mortality and a higher PAR in patients with LVEF ≥ 40% than LVEF < 40%.

Keywords: malnutrition, left ventricular ejection fraction category, all-cause mortality, interaction, population attributable risk

INTRODUCTION

Malnutrition is a common complication of several chronic illnesses, and it could accelerate the progression of the disease as part of a vicious cycle relevant to cytokine activation (1–4). Previous studies have shown that malnutrition is an important poor prognostic factor for chronic heart failure (HF) (5), advanced heart failure (AHF) (3), acute decompensated heart failure (ADHF) (6), and preserved ejection fraction (HFpEF) (7).

Current evidence has shown that poor cardiac function was related to increased production of appetite suppression, catabolic cytokines, and muscle catabolism (3, 7–9). Patients with poor cardiac function are more likely to lose appetite and have worse digestion and absorption, which can aggravate malnutrition to affect prognosis. As a result, it may lead to the stereotype that patients with good cardiac function will be considered at low risk of morbidity and mortality from malnutrition. But limited data exist on the prognostic impact of malnutrition focused on patients with good cardiac function. The relationship between nutritional status, good cardiac function and all-cause mortality has not been adequately addressed. Whether the association between malnutrition and mortality differs in patients with or without poor cardiac function is unknown. Understanding the potential interplay of the prognostic impact of malnutrition focused on patients with different cardiac functions may allow more personalized management of patients with or without poor cardiac function.

Left ventricular ejection fraction (LVEF) is reliable measurement for cardiac function evaluation (10, 11). Accordingly, our study aims to explore the relationship between malnutrition and mortality in patients with LVEF ≥ 40% and with LVEF < 40% assessed by the CONUT score in a cohort of patients undergoing coronary angiography (CAG).

METHOD

Data Sources and Study Population

The Cardiorenal ImprovemeNt (CIN) study is a retrospective observational study that enrolled 88,939 consecutive patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) in Guangdong Provincial People's Hospital, Guangdong, China, hospitalized between January 2008 to December 2018 (ClinicalTrials.gov NCT04407936). PCI was performed according to standard clinical practice guidelines. We excluded patients with missing data on follow-up and missing data of LVEF and did not meet the CONUT score. Eventually, 45,826 patients were included (**Supplementary Figure 1**). All traceable personal identifiers were erased before analysis to cover patient data confidentiality. The study was conducted according to the declaration of Helsinki and was approved by the Guangdong Provincial People's Hospital ethics committee.

Baseline Data Collection

Data were obtained from the electronic clinical management records system of the Guangdong Provincial People's Hospital. We had access to all primary and secondary medical records to view the baseline information of patients, which included demographic characteristics, comorbidities, laboratory tests, and medications at discharge. Blood samples except lipid profiles were collected at admission or before CAG and PCI. The lipid measurement was taken after an overnight fasting blood sample.

Endpoint and Clinical Definition

The primary endpoint was all-cause death which was monitored and recorded by experienced nurses and research assistants through outpatient interviews and telephones. The Controlling Nutritional Status (CONUT) score, as an assessment for the nutritional status of hospitalized patients, was originally proposed in 2005 by Ignacio de Ulibarri et al. (12). The tool incorporates serum albumin (g/L), cholesterol (mmol/L), and total lymphocyte count (10^9/L) to assess the state of malnutrition. Left ventricular ejection fraction (%) was evaluated in light of the current international recommendations. The estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease (MDRD) formula. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2 (13). Acute myocardial infarction (AMI), hypertension, and diabetes mellitus (DM) were defined using ICD-10 codes. Anemia was defined as a hematocrit ≤39% for males or ≤36% for females.

Statistical Analysis

Baseline characteristics are presented as means ± SDs for continuous variables, and proportions for categorical variables, and medians and interquartile ranges (IQRs) for non-normally distributed data. Continuous variables were tested for normal distribution by use of Kolmogorov-Smirnov test. Differences in two categories of LVEF (<40% and ≥40%) in baseline characteristics were compared through the use of Student t-test for continuous variables, chi-square tests for categorical variables,

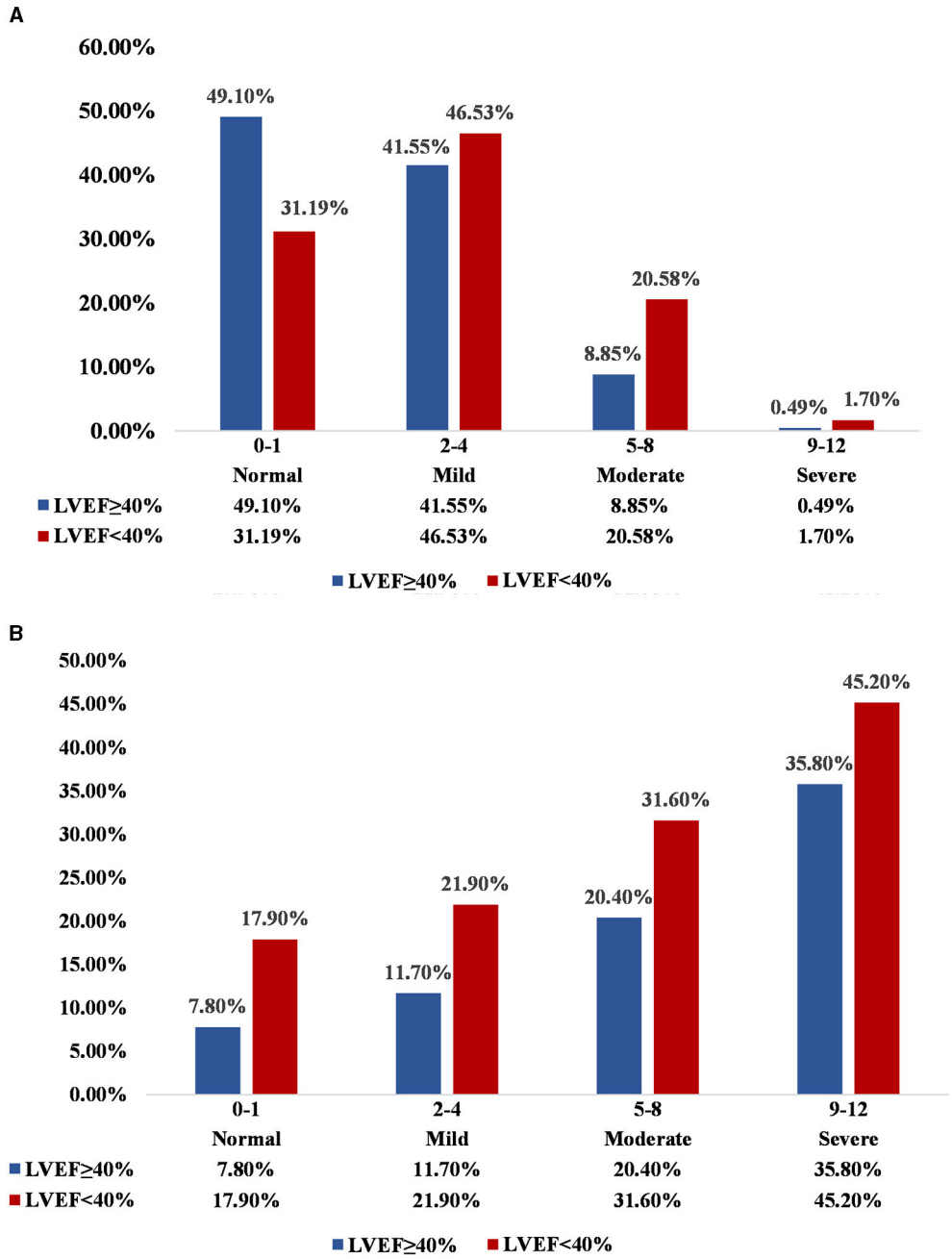

FIGURE 1 | (A) Distribution of nutritional state in LVEF ≥ 40% and LVEF < 40%; **(B)** Incidence of death across malnutrition and LVEF categories. Normal, Mild, Moderate, and Severe correspond to the state of malnutrition, respectively, based on the CONUT score. Normal: CONUT 0–1; Mild: CONUT 2–4; Moderate: CONUT 5–8; Severe: CONUT 9–12.

and Kruskal-Wallis test for non-normally distributed data. Time-to-event data were shown in graphs using Kaplan-Meier curves. The survival of each group was compared by log-rank test. Cox regression models were used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for mortality across combined LVEF and/or malnutrition categories, respectively. Models were adjusted for age, gender, hypertension (HT), DM, PCI, coronary artery disease (CAD), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TRIG), CKD, statins, atrial fibrillation (AF), anemia, and stroke. The Wald chi-square test was used to estimate the *P*-value of the interaction between LVEF

categories and malnutrition. R (ver. 4.0.3) was used in all statistical analyses.

RESULT

Patient Characteristics

Among the 45,826 patients undergoing coronary angiography enrolled, the mean age was 61.9 ± 10.3 years, 30,942 (67.5%) patients were male, 5,909 (12.9%) had AMI, 13,591 (29.7%) had anemia and a total of 21,621 (47.2%) who underwent PCI treatment. Most patients with LVEF ≥ 40% were female; used antihypertensive medications; had higher serum total cholesterol (CHOL), TRIG, HDL-C, albumin (ALB), lymph cell count (LYMPH1), Na and eGFR, and lower lipoprotein(a), white blood cell (WBC), URIC, aspartate aminotransferase (AST), pre-operative creatinine (pre-CREA) and N-terminal pro–B-type natriuretic peptide (NT-proBNP). There were no apparent differences in AF, hemoglobin (HGB) and LDL-C in the two groups. Of the patients with LVEF < 40%, mild malnutrition accounted for 46.5% and moderate to severe malnutrition for 22.3% by CONUT, while there were 41.6% in mild malnutritional status and 9.3% were in moderate to severe malnutritional status among patients with LVEF ≥ 40%. In general, the malnutrition status of the LVEF ≥40% group was better (**Figure 1A**). More information on the baseline characteristics of patients enrolled was presented in **Table 1**.

Malnutrition, LVEF Categories, and Mortality

During a median follow-up time of 4.5 years (percentile 2.8–7.1), 5,350 (11.7%) patients died. The mortality of normal, mild, moderate and severe malnutrition was 17.9, 21.9, 31.6, and 45.2%, respectively, in patients with LVEF <40%, while the mortality of normal, mild, moderate and severe malnutrition was 7.8, 11.7, 20.4, and 35.8%, respectively, in patients with LVEF ≥ 40% (**Figure 1B**). The Kaplan-Meier curve for the relationship of all-cause mortality across nutritional states categorized by LVEF was shown in **Figure 2**. Increasing the severity of malnutrition demonstrated consistently higher mortality in patients with LVEF ≥ 40% and with LVEF < 40%.

Controlling for confounding variables, worsening malnutrition status was also associated with a marked upward trend of mortality in patients with LVEF ≥ 40% (mild, moderate, and severe vs. normal, HR: [1.21 (1.12–1.31)], [1.56 (1.40–1.74)], [2.20 (1.67–2.90)], respectively, p for trend <0.001). Although there seemed to be a mildly upward trend in LVEF<40% group, it was not significant (mild, moderate, and severe vs. normal, HR: [1.00 (0.83–0.98)], [1.20 (0.95–1.51)], [1.41 (0.87–2.29)], respectively, p for trend >0.05). In our study, the highest risk of mortality was present in malnourished patients with LVEF < 40%. However, it was unexpected that patients with LVEF ≥ 40% had a higher malnutrition-associated risk of mortality than those with LVEF < 40% (p for interaction <0.001) (**Figure 3**). More details of the individual contribution to mortality of all the other variables tested in the multivariate models were shown in **Supplementary Table 1**. PAR for all-cause mortality in CAG patients was greater for different degrees of malnutrition in LVEF ≥ 40% (normal [ref], mild [9.0%], moderate [18.4%] and severe malnutrition [9.1%]) than those in LVEF<40% (normal [0.6%], mild [3.0%], moderate [5.4%] and severe malnutrition [3.1%]) (**Figure 4**).

DISCUSSION

To our knowledge, this is so far the first largest real-world study to analyze the correlation of malnutrition and all-cause mortality in different LVEF categories. The findings from the present study were that malnutrition was common in CAG patients, and the relationship was unparallel between nutritional status and all-cause mortality in LVEF ≥ 40% and LVEF < 40%. Degrees of malnutrition can stratify the risk of mortality in patients with LVEF ≥ 40%, while malnutrition stratification did not appear to predict mortality risk in patients with LVEF < 40%. This inspired that nutritional intervention may be more effective in patients with relatively good cardiac function.

The first issue to highlight is the prevalence of malnutrition. We chose to study the CONUT score, which is considered as an effective tool for identifying malnutrition in patients (12). The main advantage of this score lies in the fact that it uses only albumin, cholesterol and lymphocyte levels to calculate, which can be computed from parameters readily available on routine testing, eliminating the need for anthropometric measurements. Based on the CONUT score, we discovered a large proportion of our patients suffered from malnutrition. Sixty-nine percent of patients with LVEF <40% were malnutrition (47% in mild malnutrition status, 22% in moderate to severe malnutrition status) and 51% were in malnutritional status (42% in mild malnutrition, 9% in moderate to severe malnutrition) among patients with LVEF ≥ 40%. Previous studies had reported that malnutrition was an important comorbidity in patients with poor cardiac function. Agra Bermejo et al. (1) indicated that 67% of patients with heart failure suffered from malnutrition using the CONUT score among 145 Spanish with an average age of 69.6 years. Iwakami et al. also showed that 78% of patients with an average age of 75 years from Japan were in bad nutritional status based on the CONUT score among a cohort of 635 AHF patients (14). However, few studies pay attention to the prevalence of malnutrition in patients with relatively good cardiac function currently. In our research, a high prevalence of malnutrition was discovered in patients with LVEF ≥ 40%. Nearly half of them were in a malnourished status, suggesting that malnutrition may be one of the most important comorbidities for patients with relatively good cardiac function. Therefore, our research supports the necessity of malnutrition screening in all patients hospitalized for CAG with LVEF ≥ 40% and with LVEF < 40%. Attention should be paid not only to the nutritional status of patients with LVEF < 40% but also to that in patients with LVEF ≥ 40%.

The second issue that needs to be assessed is the relationship between malnutrition and mortality. Surprisingly, degrees of malnutrition were still related to all-cause death in CAG patients with LVEF ≥ 40% after controlling for confounders in our research. According to studies conducted by Sze et al. (15),

TABLE 1 | Baseline characteristics of study patients across LVEF categories.

Characteristics	Overall cohort	LVEF ≥ 40%	LVEF < 40%	*P*-value
	***n* = 45,826**	***n* = 42,181**	***n* = 3,645**	
Demographic characteristics				
Age, year	61.9 ± 10.3	61.8 ± 10.3	62.7 ± 10.9	<0.001
Male, *n* (%)	30,942 (67.5)	28,041 (66.5)	2,901 (79.6)	<0.001
Medical history				
AMI, *n* (%)	5,909 (12.9)	5,244 (12.4)	665 (18.3)	<0.001
CHF, *n* (%)	4,870 (10.6)	3,601 (8.5)	1,269 (34.8)	<0.001
Anemia, *n* (%)	13,591 (29.7)	12,282 (29.1)	1,309 (35.9)	<0.001
Hypertension, *n* (%)	22,729 (49.6)	21,120 (50.1)	1,609 (44.2)	<0.001
DM, *n* (%)	10,153 (22.2)	9,041 (21.4)	1,112 (30.5)	<0.001
PCI, *n* (%)	21,621 (47.2)	19,629 (46.5)	1,992 (54.7)	<0.001
CKD, *n* (%)	7,485 (16.3)	6,259 (14.8)	1,226 (33.6)	<0.001
COPD, *n* (%)	347 (0.8)	303 (0.7)	44 (1.2)	<0.001
AF, *n* (%)	4,394 (9.6)	4,053 (9.6)	341 (9.4)	<0.001
Laboratory tests				
Lipoprotein(a), mg/dL	151.34 [82.00, 318.16]	149.00 [80.92, 312.42]	184.57 [98.94, 389.00]	<0.001
WBC, 10^9/L	7.68 ± 2.55	7.63 ± 2.51	8.16 ± 2.90	<0.001
HGB, g/L	133.14 ± 16.88	133.18 ± 16.63	132.74 ± 19.51	0.132
CHOL, mmol/L	4.59 ± 1.18	4.60 ± 1.18	4.48 ± 1.20	<0.001
TRIG, mmol/L	1.61 ± 1.17	1.62 ± 1.19	1.44 ± 0.88	<0.001
APOB, g/L	0.86 ± 0.24	0.86 ± 0.24	0.88 ± 0.24	0.002
LDL-C, mmol/L	2.84 ± 0.94	2.84 ± 0.94	2.85 ± 0.98	0.564
HDL-C, mmol/L	1.03 ± 0.28	1.04 ± 0.28	0.97 ± 0.27	<0.001
HbA1c, %	6.37 ± 1.30	6.34 ± 1.27	6.69 ± 1.48	<0.001
URIC, μmol/L	400.65 ± 115.76	394.96 ± 110.62	466.74 ± 148.82	<0.001
ALB, g/L	36.77 ± 4.17	36.93 ± 4.10	34.85 ± 4.59	<0.001
LVEF, %	60.22 ± 12.06	62.69 ± 8.84	31.60 ± 5.80	<0.001
LYMPH, 10^9/L	1.96 ± 0.74	1.98 ± 0.74	1.77 ± 0.70	<0.001
Na, mmol/L	139.15 ± 2.94	139.23 ± 2.88	138.31 ± 3.40	<0.001
AST, IU/L	24.00 [20.00, 33.00]	24.00 [20.00, 32.00]	27.00 [21.00, 42.00]	<0.001
ALT, IU/L	22.00 [16.00, 33.00]	22.00 [16.00, 33.00]	25.00 [17.00, 41.00]	<0.001
pre-CREA, μmol/L	84.80 [71.08, 101.00]	83.70 [70.60, 99.00]	99.00 [83.00, 123.56]	<0.001
NT-proBNP, pg/ml	250.50 [63.19, 1083.00]	195.50 [56.84, 821.40]	2577.00 [1162.00, 5582.00]	<0.001
eGFR, mL/min/1.73m^2	78.84 ± 24.12	79.90 ± 23.81	67.51 ± 24.50	<0.001
Medications				
ACEI or ARB, *n* (%)	17,589 (39.5)	15,729 (38.3)	1,860 (52.9)	<0.001
Beta-blockers, *n* (%)	30,545 (68.5)	27,749 (67.6)	2,796 (79.5)	<0.001
Statins, *n* (%)	33,730 (75.7)	31,022 (75.6)	2,708 (77.0)	<0.001
Follow-up date, day	1893.03 ± 1090.91	1911.1 ± 1082.81	1683.43 ± 1160.41	<0.001
CONUT group, *n* (%)				
Normal	21,849 (47.68)	20,712 (49.10)	1,137 (31.19)	<0.001
Mild	19,223 (41.95)	17,527 (41.55)	1,696 (46.53)	
Moderate	4,485 (9.79)	3,735 (8.85)	750 (20.58)	
Severe	269 (0.59)	207 (0.49)	62 (1.70)	

Values are, n (%), mean ± SDs, or median [IQRs]. AMI, acute myocardial infarction; CHF, congestive heart failure; DM, diabetes mellitus; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; HGB, hemoglobin; CHOL, serum total cholesterol; TRIG, triglycerides; APOB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; ALB, albumin; LVEF, left ventricular ejection fraction; LYMPH, lymph cell count; Na, sodium,; AST, aspartate aminotransferase; ALT, alanine aminotransferase; pre-CREA, pre-operative creatinine; NT-proBNP, N-terminal pro–B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI or ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocke; CONUT, Controlling Nutritional Status. CONUT scores: CONUT 0-1, normal nutritional status; CONUT 2–4, mildly malnourished; CONUT 5–8, moderately malnourished; CONUT 9–12, severely malnourished.

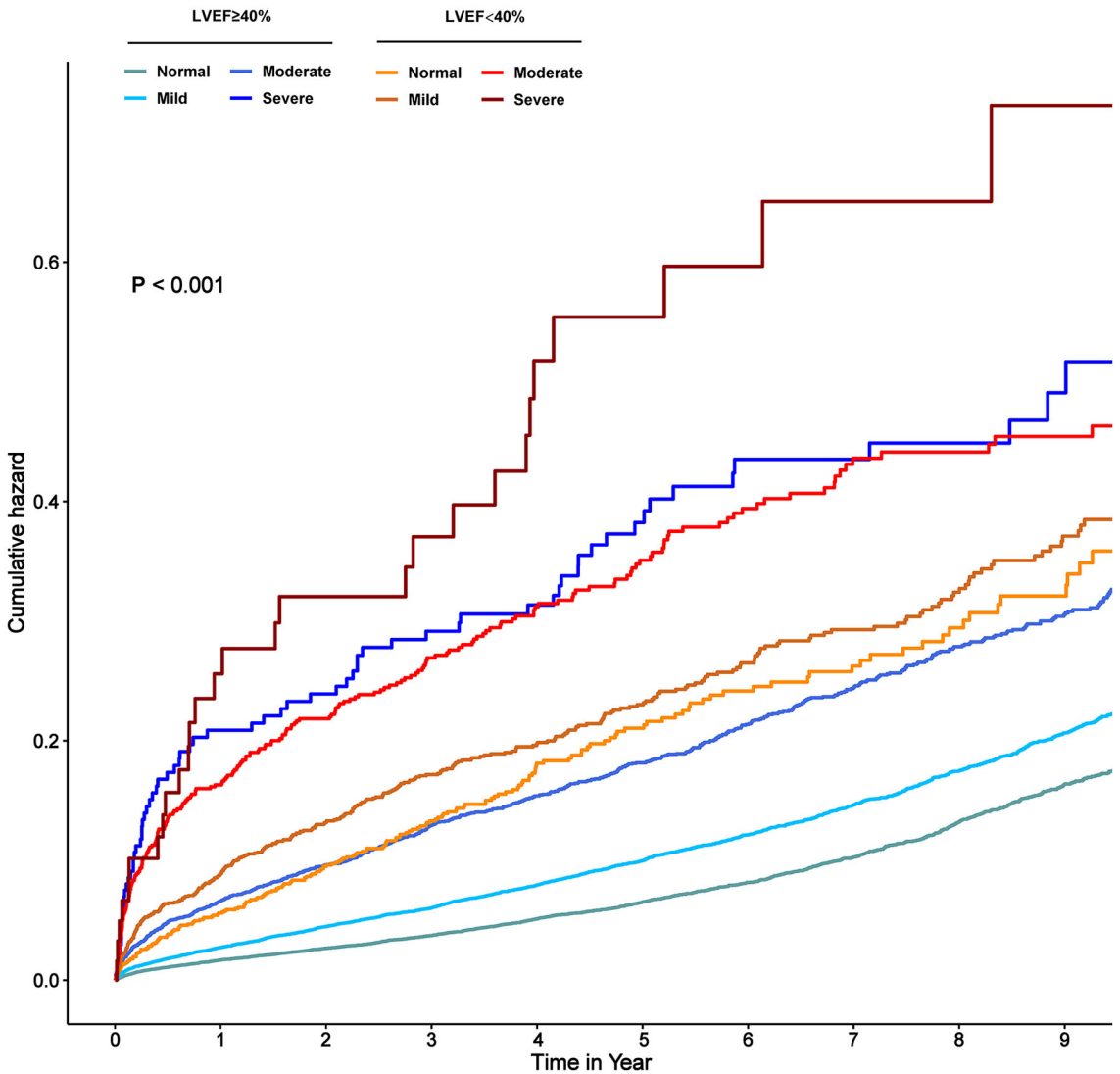

FIGURE 2 | Kaplan–Meier curve in terms of all-cause mortality in normal, mildly, and moderate to severe malnourished patients with and without LVEF < 40%. Normal, Mild, Moderate, and Severe correspond to the state of malnutrition, respectively, based on the CONUT score. Normal: CONUT 0–1; Mild: CONUT 2–4; Moderate: CONUT 5–8; Severe: CONUT 9–12.

worsening malnutrition was associated with worse outcomes in British patients with HF using three scoring systems (Geriatric Nutritional Risk Index—GNRI, the CONUT score and Prognostic Nutritional Index—PNI). Additionally, Minamisawa et al. (7) also proved that malnutrition evaluated by the GNRI was an important factor affecting all-cause death which should not be neglected in patients with HFpEF. However, previous studies were only focused on the relation between malnutrition and mortality in patients with poor cardiac function. Indeed, we found that malnourished patients have a higher mortality rate than those with normal nutrition among patients with LVEF $\geq$ 40%. Although the highest risk of mortality was present in malnourished patients with LVEF < 40%, it is important to note that patients with LVEF $\geq$ 40% have a higher malnutrition-associated risk of mortality. What's more, in our study, we found that variables with significant hazard ratios in the Cox regression analysis between different LVEF categories were also different, among of which, gender, CAD, LDL-C, Statins, AF, and Stroke variables had significant hazard ratios in the Cox regression analysis in LVEF $\geq$ 40% group, but not in the LVEF < 40% group. This suggests that we may need to pay more attention to these variables with significant hazard ratios in patients with LVEF $\geq$ 40%. Clinical malnutrition screening and intervention should be attached great importance to CAG patients with LVEF $\geq$ 40% and with LVEF < 40%.

The mechanistically plausible explanations for the association among malnutrition, cardiac function and mortality in patients

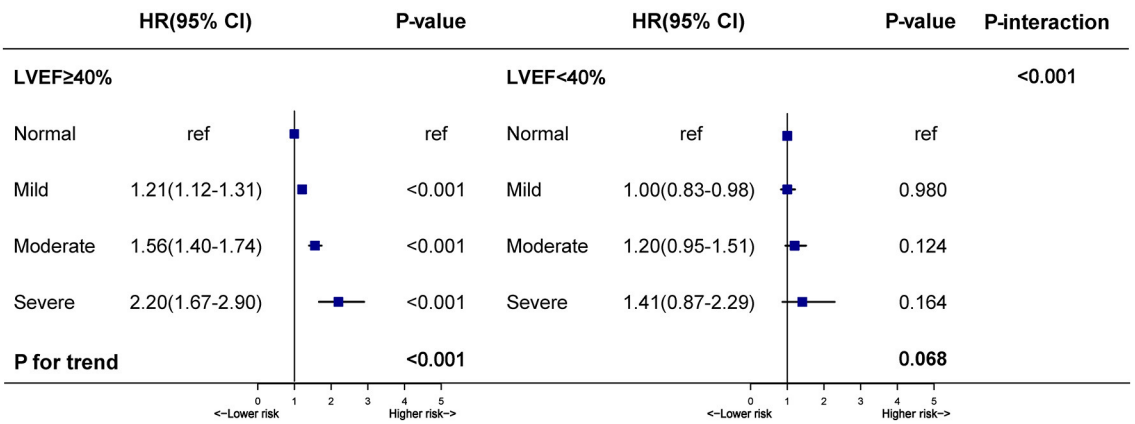

FIGURE 3 | Hazard ratios for all-cause mortality stratified by the nutritional state in patients with LVEF ≥ 40% and LVEF < 40%. Model adjusted for age, gender, percutaneous coronary intervention; hypertension; diabetes mellitus; anemia; stroke; coronary artery disease; chronic kidney diseases; atrial fibrillation; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; triglycerides and statins. *p-value for interaction test: 2-way interaction of malnutrition (normal vs. mild, moderate, and severe) were severely malnourished and LVEF categories (LVEF ≥ 40% vs. LVEF < 40%).

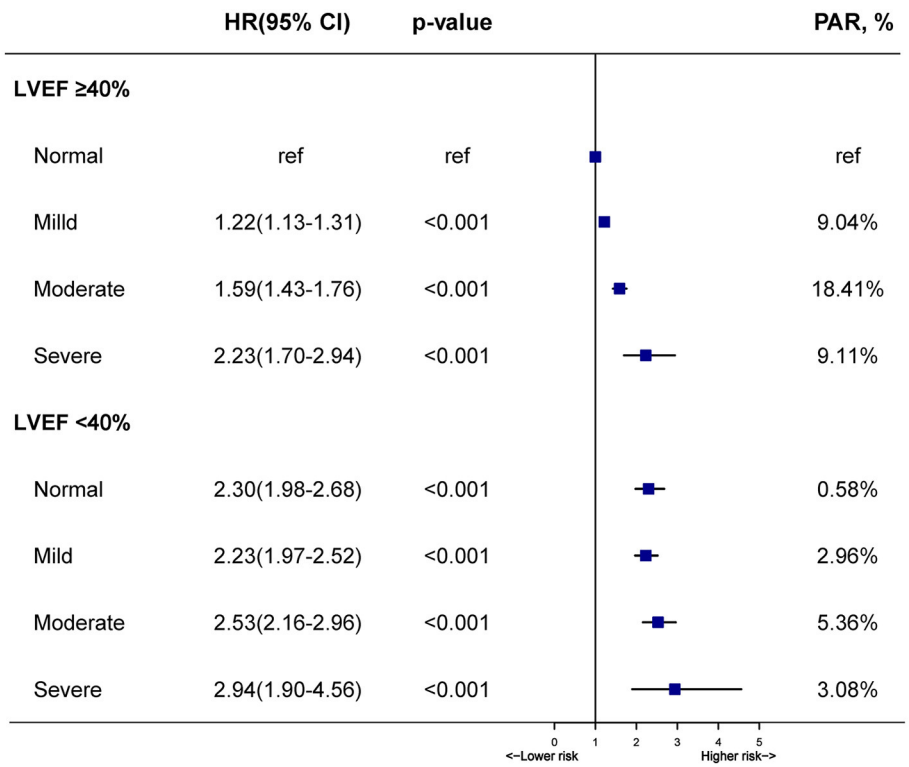

FIGURE 4 | Hazard ratios and population-attributable risk for all-cause mortality across malnutrition and LVEF categories. Model adjusted for age, gender, percutaneous coronary intervention, hypertension, diabetes mellitusc, anemia, stroke, coronary artery disease, chronic kidney diseases, atrial fibrillation, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and statins.

with CAG are as follows. For patients with poor cardiac function, LV dysfunction caused the release of natriuretic peptides (16), which stimulated lipolysis of adipose tissue (17), and indirectly stimulated the secretion of adiponectin to promote glucose and fatty acid utilization (18), resulting in weight loss and increased burden of death. Metabolites and cytokines released under malnutrition may adversely affect cardiac performance (19) which may also contribute to mortality. Another likely explanation for the high mortality of malnutrition is that nutritional status may correlate with inflammation (20, 21).

The increased risk of mortality is because chronic inflammatory diseases were connected with muscle catabolism, catabolic cytokines, albumin consumption and appetite suppression (21). In addition, frailty may be a potentially important link mediating an association between malnutrition and poor health outcomes (22). The likely explanation for the interaction between LVEF categories and malnutrition-associated mortality in our study is that patients with LVEF < 40% at baseline were more likely to be weaker and their conditions at baseline were poorer, thereby associating with a relatively high level of mortality. The impact of malnutrition may be hidden by stronger competing risk factors (LVEF < 40%) for mortality. Owing to the effect, the contribution of malnutrition to prognosis was relatively reduced, and the influence of malnutrition-related mortality was relatively flat. As for those with relatively good cardiac function, their all kinds of body functions were more active, more likely to respond to changes in malnutrition, and more vulnerable to changes in malnutrition, which may cause a rapid increase in the risk of mortality in malnutrition.

Based on our findings, clinicians are strongly recommended to conduct early identification, preventive treatment, nursing management and pharmacologic treatment for the impact of malnutrition on prognosis in CAG patients with different categories of LVEF (23). Screening CAG patients with different categories of LVEF for malnutrition in hospital may identify patients at high risk of adverse outcomes to help them tailor individual treatment on time. At present, the main recommendations of intervention measures in the guidelines for malnourished patients include changing diet, enhancing exercise, and nutritional supplements (24). For malnourished patients with LVEF ≥ 40%, malnutrition may be more easily improved and they are more likely to benefit after improvement. A number of multidisciplinary strategies encourage these patients to accept oral nutritional supplements, food/fluid fortification or enrichment, dietary counseling, and educational interventions to improve their malnutrition state (25). For malnourished patients with LVEF < 40%, heart treatment is mainly taken and nutrient supplement is the secondary auxiliary means. Entresto is approved by United States Food and Drug Administration (US FDA) for heart failure treatment. It is verified as an effective therapy in treating heart failure with reduced LVEF (26). Similarly, CRT and SGLT2i are two effective therapies for HFrEF which can improve the quality of life as well as reduce the rate of heart failure hospitalizations and mortality (27, 28). Moreover, physicians should keep up with the current scientific evidence to combine with their clinical experience to offer the most advantageous, personalized, and optimal protective treatment.

LIMITATION

Nevertheless, there are some limitations to this study. First, because it is a single-center, observational study, our findings didn't reflect direct causation. We must always be aware of the potential for residual and uncontrolled confounding which may explain the correlation to some extent. Due to the observational study design, it is necessary to conduct a prospective clinical trial. Unfortunately, information on socioeconomic characteristics, height, weight and/or body composition that might help us understand malnutrition in multiple dimensions was not available. Second, it's essential to further compare the value of the CONUT score tool on the prognosis of patients with other comprehensive malnutrition scoring tools for the reason that malnutrition is a complex problem, especially in elders, which is caused by a variety of factors. Furthermore, our data did not collect information on causes of death, so we cannot directly determine which causes of mortality were directly related to malnutrition. Finally, we only included Chinese individuals that might be restricted regarding generalization across ethnicities; however, we are not aware of whether any data in this study are applicable for other people of most ethnicities. More studies from different countries with other health management and social systems are indispensable to confirm these findings by other researchers.

CONCLUSION

Malnutrition is common in CAG patients with LVEF ≥ 40% and LVEF < 40%. Unexpectedly, our findings indicate that malnutrition has a greater effect on prognosis and a higher PAR in patients with LVEF ≥ 40% than LVEF<40%. Greater attention needs to be given to malnutrition in patients with LVEF ≥ 40%. The findings can be translated into further researches to optimize the outcomes at risk stratification through malnutrition and the LVEF category.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available due to the institution policy but are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Guangdong Provincial People's Hospital ethics committee and the study was performed according to the declaration of Helsinki. The ethics committee waived the requirement of written informed consent for participation because our review was a retrospective study of data reuse.

AUTHOR CONTRIBUTIONS

ZM, ZH, and WL: research idea and study design. HL and BW: data acquisition. QH: data analysis/interpretation. SC: statistical analysis. SC, SZ, and YLia: supervision and mentorship. JL, SC, YLiu, and JC: writing guidance. All authors contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions on the accuracy or integrity of any

portion of the work are appropriately investigated and resolved, read and approved the final version.

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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.2021.740746/full#supplementary-material

Supplementary Figure 1 | Flow of patients through the study. CONUT, Controlling Nutritional Status score; LVEF, Left ventricular ejection fraction.

Supplementary Table 1 | Hazard ratios for all-cause mortality stratified by the nutritional state in patients with LVEF $\geq$ 40% and LVEF $<$ 40%.

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Impact of Branched Chain Amino Acid on Muscle Mass, Muscle Strength, Physical Performance, Combined Survival, and Maintenance of Liver Function Changes in Laboratory and Prognostic Markers on Sarcopenic Patients With Liver Cirrhosis (BCAAS Study): A Randomized Clinical Trial

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Background: This study aimed to investigate the long-term effects of branched-chain amino acids (BCAAs) supplementations on the parameters associated with improved prognosis in sarcopenic patients with liver cirrhosis (LC) and evaluate its impact on cirrhotic-related events.

Methods: A 24-week, single-center, randomized, open-label, controlled, two cohort parallel-group intervention study was carried out by comparing the efficacy of BCAAs against lactoalbumin (L-ALB) on 106 sarcopenic patients with LC. The BCAA (intervention) group was treated with 7.2 g BCAA per dose, whereas the L-ALB group was treated with 6.3 g of L-ALB. The primary outcome was to assess the effect of BCAA on the parameters of sarcopenia, such as muscle mass, muscle strength, and physical performance. The secondary outcomes were to study the combined survival and maintenance of liver function changes in laboratory and prognostic markers over the duration of 6 months.

Results: The treatment with BCAA leads to the significant improvement in sarcopenic parameters, such as muscle strength, muscle function, and muscle mass. The total

cirrhotic-related complications and cumulative event-free survival occurred fewer in the BCAA group than in the L-ALB group. In addition, prognostic markers improved significantly in the study.

Conclusion: The current study demonstrated that long-term BCAAs supplementation improved sarcopenia and prognostic markers in patients with advanced LC.

Keywords: sarcopenia, liver cirrhosis, branched-chain amino acid, albumin, quality of life

INTRODUCTION

The liver is a prime site for biochemical pathways responsible for nutrient metabolism. Cirrhosis-related liver dysfunction results in nutritional diseases, such as sarcopenia, which indicates severe muscle protein depletion (1, 2). Furthermore, sarcopenia is a syndrome characterized by progressive and generalized loss of muscle mass, which also accounts as a major predictor for morbidity and mortality in people with liver cirrhosis (LC) (3). Indeed, sarcopenia is one of the most commonly prevalent metabolic complication which is associated with reduced levels of branched-chain amino acids (BCAAs) (3–5). Patients with LC are in the hypermetabolic state as their energy generation pattern after an overnight fast is parallel to that observed in healthy individuals after 2–3 days of starvation (5, 6). Such a catabolic state increases the depletion of amino acids and accelerates the breakdown of skeletal muscle to release amino acids with disruption of muscle balance, resulting in sarcopenia (7–9). The poor prognosis of sarcopenia adversely affects the survival, health-related quality of life, and response to any underlying infection.

Recent studies conclude that BCAAs preparations have been proposed to be effective in improving the body composition by correcting the amino acid imbalance in the blood in patients with decompensated cirrhosis (10). However, most of the studies are conducted on a small sample size with multiple parameters, such as different complications of LC (11). Hence, there is an utmost need for a longitudinal study to assess the impact of BCAA, as the Indian population is experiencing a temporal trend on patients with sarcopenic cirrhosis (12).

In this regard, we report the long-term benefits of BCAA on the parameters associated with improved prognosis in sarcopenic patients with LC. Additionally, we have evaluated its impact on the cirrhotic-related events.

METHODS

Study Design and Setting

A 24-week, single-center, randomized, open-label, controlled, two cohort parallel-group intervention study on the LC was carried out in the Department of Gastroenterology, National Institute of Medical Sciences and Research, NIMS University Rajasthan, Jaipur, India, from April 2019 to October 2020. The protocol was conformed in accordance with the 1,975 principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (IEC No NIMSUNI/IEC/217/22) (3) and was registered under Clinical Trials Registry—India (CTRI/2020/04/024762). Each participant was informed in detail about the purpose of the study, and the treatment was fully explained to all participants before obtaining informed consent. The manuscript conformed to the Consolidated Standards of Reporting Trials Statement 2010 (CONSORT 2010 Statement) to improve the quality of reporting.

Participants

In this study, the population consisted of patients with cirrhosis who met the inclusion and exclusion criteria. The inclusion criteria were: diagnosis of LC based on the clinical and laboratory data and/or liver biopsy specimens, Child-Turcotte-Pugh Score (CTP) $\geq$ 7 and $<$ 12 (class B or C), radiological and endoscopic evidence of portal hypertension with sarcopenia, according to the cut-off values of European Working Group on Sarcopenia in Older People 2, 2018 (EWGSOP2) (13), the ability to stand with or without support, receipt of adequate nutrition (sufficient energy intake according to the requirements set by a registered dietitian), and provision of informed consent. The exclusion criteria were as followed: active alcohol intake (in the past 6 weeks), active malignant disease, overt hepatic encephalopathy, severe/refractory ascites, CTP score $\geq$ 12, active gastrointestinal bleeding, renal failure (serum creatinine$>$ 1.5 mg/dl), brittle diabetes mellitus, psychiatric/neurological problems, hepatocellular carcinoma, history of a previous transjugular intrahepatic portosystemic shunt, marked symptomatic comorbidities (cardiac, pulmonary, and renal), and non-compliance with treatment.

Intervention Protocol

Patients after fulfilling the baseline evaluation were randomized and sub-classified into two groups, lactoalbumin (L-ABL) group and BCAA group, for supplement provision. Both the sachets (active and placebo) weighed equally (10 g). Explicitly, BCAA (active treatment) weighed 8.1 g containing 1.2 g L-leucine, 0.6 g L-isoleucine, and 0.6 g L-valine and saccharose (5.7 g) for a total energy supply of 37.5 kcal. The L-ABL group weighed 9.1 g, which consisted of 2.1 g L-ALB (90.3 mg valine, 226.8 mg of leucine, and 126 mg iso-leucine) with 4.0 g saccharose, and 3.0 g mannitol for a total of 33.6 kcal/packet (supplied by—Medisys Biotech Pvt Ltd, Sirmour, Himachal Pradesh, India) (11). The patients were randomized into the BCAA and L-ALB group in a 1:1 ratio using a simple randomization method (Microsoft Excel 2010; Microsoft Corporation, Washington DC, WA, USA). During the study period, the total energy and protein were kept at 30–35 kcal kg^{-1} d^{-1} and 1.5 g protein kg^{-1} d^{-1} through the provided supplement. With all, the nutritional supplementations

TABLE 1 | Baseline clinical characteristics of 138 patients enrolled in the study.

Characteristics	BCAA group (*N* = 69)	L-ALB group (*N* = 69)
Age (year)	43.69 ± 15.50	48.02 ± 13.02
Male	60 (86.95)	58 (84.05)
Weight (Kg)	55.04 ± 6.27	55.40 ± 9.84
Body Mass Index (Kg/m^2)	21.06 ± 2.65	22.09 ± 3.54
Etiology (Alcohol/ Viral/ Autoimmune/ Cryptogenic)	51/11/1/6	46/13/4/6
Ascites (Mild/Moderate/Severe)	11/35/11	12/15/24
Child-Turcotte-Pugh Score	10.22 ±1.44	10.74 ± 1.43
Child-Turcotte-Pugh Class B/C	33/36	34/35
MELD	13.89 ± 2.31	13.81 ± 3.05
Hepatic Encephalopathy (None/Grade I/Grade II)	48/12/9	46/13/10
ALT	30.0 (18–40)	29 (17–41)
AST	68 (33–112)	65 (32–109
Ammonia	71 (40–122)	67 (51–116)
INR	1.60 (1.30–1.86)	1.51 (1.26–1.91)

Values are expressed in mean and SD (Mean ±SD), number and percentage n (%), and median and interquartile range (IQR).
MELD, Model for End-Stage Liver Disease; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio.

TABLE 2 | Baseline characteristics of 106 patients who completed the study till 24 weeks.

Characteristics	BCAA group (*N* = 52)	L-ALB group (*N* = 54)	*p*-value*
Age (year)	43.05 (15.01)	47.18 (13.07)	0.983
Male	43 (83.69)	44 (81.48)	0.052
Weight (Kg)	55.26 (6.30)	54.24 (7.78)	0.934
Body Mass Index (Kg/m^2)	21.16 (2.76)	21.53 (3.09)	0.996
Etiology (Alcohol/ Viral/ Autoimmune/ Cryptogenic)	39/8/1/4	36/11/0/7	0.061
Ascites (Mild/Moderate/Severe)	8/23/21	7/24/22	0.052
Hepatic Encephalopathy (None/Grade I/Grade II)	40/8/4	39/10/5	0.049
Child-Turcotte-Pugh Score	9.41 ± 1.52	9.69 ± 1.49	0.540
Child-Turcotte-Pugh Class B/C	33/36	34/28	0.621
MELD	13.64 ± 2.61	13.81 ± 3.13	0.810
ALT	29 (19–40)	29 (18–40)	0.218
AST	68 (33–110)	64 (32–105)	0.079
Ammonia	71 (40–122)	68 (52–118)	0.021
INR	1.62 (1.31–1.89)	1.52 (1.28–1.92)	0.995

Values are expressed in mean and SD (Mean ± SD), number and percentage n (%), and median and interquartile range (IQR).
MELD, Model for End-Stage Liver Disease; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio.
**Statistically significant at $p < 0.05$.*

were closely equicaloric and equi-nitrogenous, according to the 57th recommendation of European Society of Parenteral and Enteral Nutrition guidelines (14). During the whole experimental period, participants recorded their nutritional supplement intake timing and amount in the paper log provided by the investigators. The compliance to the treatment was assessed after counting the number of packets left in the original packet by the investigator in the follow-up, $\geq$ 90% adherence was kept adequate to continue with the eligibility.

Outcomes

The primary outcomes of the study were to assess the impact of BCAA on the parameters of sarcopenia, such as muscle mass, muscle strength, and physical performance. The secondary outcomes were to study the combined survival and maintenance of liver function, weighed through death or deterioration to exclusion criteria with changes in the clinical laboratory, and prognostic markers in the duration of 6 months.

Baseline and Follow-Up Clinical Assessment and Investigations

An overview of data collection (demographic and clinical) characteristics of baseline allocation in both the groups is given in **Table 1**. The patients were instructed to visit the department of gastroenterology for a consecutive period for further follow-up. After confirmation of diagnosis, all the assessments were conducted during the enrollment considered as a baseline followed by the 12 and 24th week.

Anthropometric Assessments

The subjects were weighed and measured for height to calculate the body mass index (BMI = actual weight [kilogram]/ height [meter square]). The triceps skinfold (TSF) was measured in millimeters using a skinfold caliper (Harpenden–weight (with case): 3 pounds (1.8 kg); Dial Graduation: 0.20 mm; measuring range: 0–80 mm; measuring pressure: 10 g mm^{-2} (constant over range); accuracy: 99%; repeatability: 0.20 mm). Mid-upper arm circumference (MUAC) was measured in centimeters, using soft fiberglass tape (Foshan Guo's Wintape Measuring Tape Co., Ltd., Guangdong, China Length: 762 mm Width: 2.5 mm), which is wrapped around the mid-upper arm at the mid-point between the olecranon and the acromial process. After obtaining the values of TSF and MUAC, mid-arm muscular circumference (MAMC) was calculated using the formula: MUAC (centimeters) – [TSF (millimeters) × 0.314]. The average of three consecutive measurements was then recorded and included in the analysis. An anthropometric evaluation was performed according to the manual of the International Society for the Advancement of

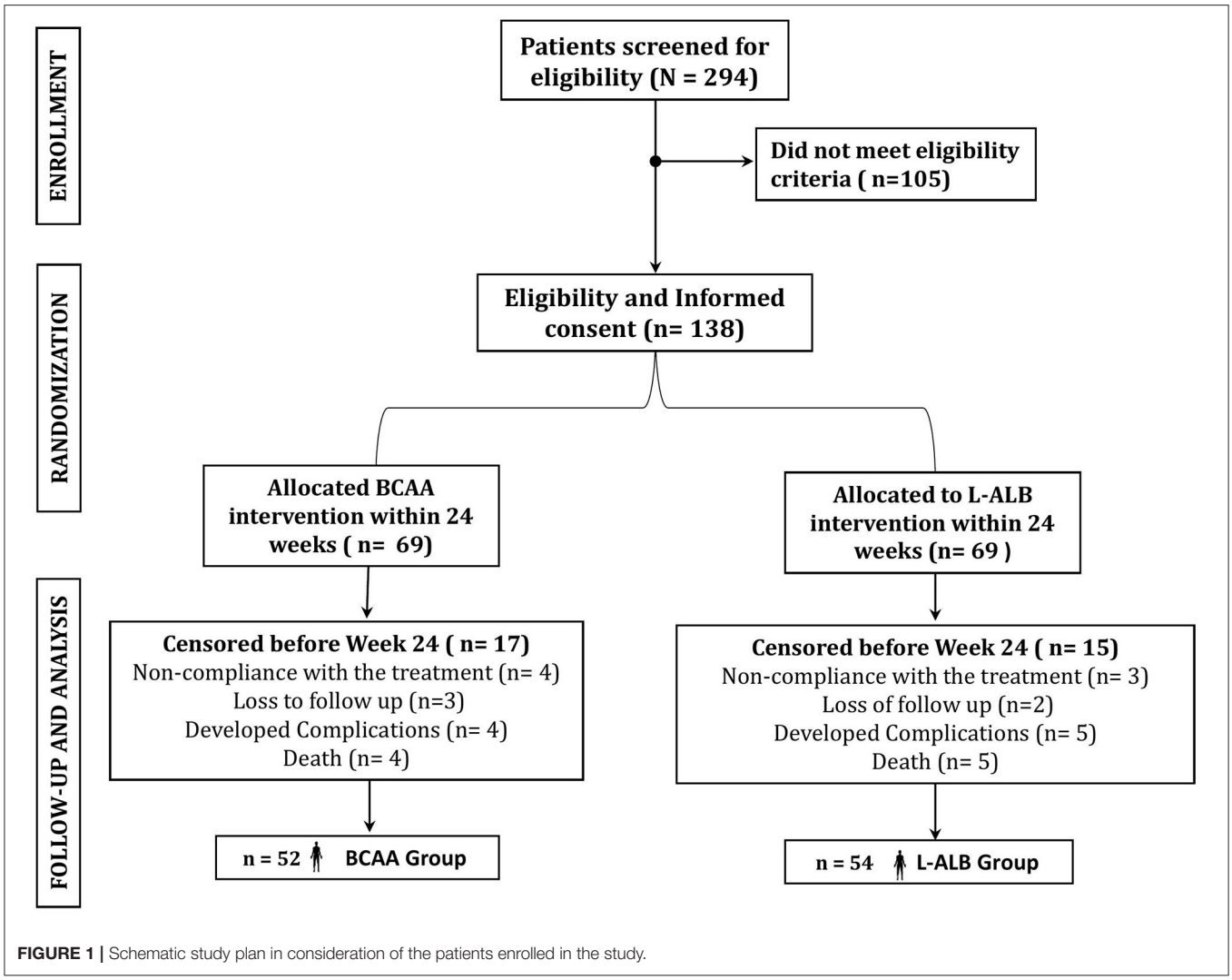


FIGURE 1 | Schematic study plan in consideration of the patients enrolled in the study.

Kinanthropometry (ISAK) return (15). The values obtained were compared with the reference values of the National Health and Nutrition Examination Survey (NHANES) on Frisancho tables to classify significant malnutrition status in the enrolled patients (16, 17).

The muscle strength was assessed by hand grip strength (HGS) using a hand dynamometer [Takei TKK 5401 Digital Handgrip Dynamometer, Takei, Niigata-City, Japan, measuring range: 5.0–100 kgf, accuracy: ± 2.0 kgf, dimensions: ∼154 (W) × 235 (D) × 62 (H)mm, and weight: ∼0.63 kg]. HGS was expressed in kilograms with two decimals. Measuring grip strength is a powerful and simple measure to assess muscle strength (18, 19). The average of three consecutive measurements was then recorded and included in the analysis. Gait speed was assessed using a modified 6-m walk test in a standardized manner to assess the physical performance (20, 21). Low grip strength corresponds to cut-off points $<26\,kg\,m^{-2}$ for men and $<18\,kg\,m^{-2}$ while low gait speed was predicted with $<0.8\,m\,s^{-1}$. The muscle quantity was measured using MRI, which is considered a gold-standard, non-invasive method for muscle mass assessment. MRI is a universally recognized method to quantify detailed tissue structure and composition, facilitating the quantification of muscle volume. The area was calculated using MRI imaging by a trained operator, with image AsanJ-Morphometry software (Asan Image Metrics, Seoul, Korea) that was developed for abdominal muscle and fat area measurements based on ImageJ (NIH, Bethesda, MD, USA). Total abdominal muscle area (TAMA) was measured at the L3 vertebral level for the diagnosis of low muscle mass with sarcopenia specific cut-off (male and female cut-off values for SMI at <50 and <39 $cm^2\ m^{-2}$, respectively). Sarcopenia was defined as low muscle strength, low muscle quantity, and low physical performance as per the updated European Working Group on Sarcopenia in Older People 2, 2018 (EWGSOP2) (13).

Laboratory and Prognostic Markers Assessment

Laboratory tests, such as serum albumin, serum creatinine, total bilirubin, serum alanine aminotransferase, serum aspartate aminotransferase, and international normalized ratio (INR) were performed. The severity of liver disease was defined using the

CTP score and Model for End-Stage Liver Disease (MELD) using laboratory parameters (17, 22).

Statistical Analysis

The previous study on enriched BCAA supplementation on sarcopenic patients reports 25% improvement in the grip strength (23). According to those estimates, with G-power software, we calculated a sample size of 54 in each group with 80.0% statistical power to observe the effect size 0.5, and two-sided effect in pre-and post-intervention matched pairs with β error of 20%. With the expectation of a 10% drop-out rate due to further deterioration of liver function or development of unpredictable complications, the final sample size was kept at 59 in both the groups.

Baseline characteristics were compared between the two study groups using the Fischer's test for categorical variables and the Mann–Whitney's test for quantitative variables. The changes in the MELD score, CTP score, serum albumin, and bilirubin levels were analyzed using a mixed linear model. The cumulative survival event-free survival (EFS) rates were estimated using the Kaplan–Meier analysis and compared using the log-rank Mantel–Cox test and the Cox-proportional regression model was used to identify the factors that contributed to the prognosis of each patient. The patients were censored when they dropped out of the study (because of hepatocellular carcinoma, death, variceal hemorrhage, or any other reason). Changes in results are expressed in mean ± SD, median (range), or frequencies. $P < 0.05$ was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences for Windows (software version 25; IBM Corporation, Armonk, NY, USA).

RESULTS

Characteristics of Patients and Clinical Course

In this study, 294 patients were screened for eligibility as per protocols. Initially, altogether 138 patients were enrolled in the study (**Table 1**), out of which only 106 patients completed the study with regular follow-up till 24 weeks (52 in the BCAA group and 54 in the L-ALB group) (**Table 2**). There is no significant difference between the demographic, mean baseline, and clinical characteristics of both arms. The overall completion rate was close to 76.81%, with a drop-out of 23.18%. During the study, 18 patients were censored (non-compliance: seven, loss of follow-up: five, developed complications: nine, and death: nine). Seven patients who withdrew for non-compliance mentioned the poor-palatability of nutritional supplementation as a reason behind the withdrawal (four in the BCAA group vs. three in the L-ALB group). Non-compliance occurred within the first 3 months of the treatment except in the L-ALB arm, in which two patients declined for further treatment after 3 months of the treatment (**Figure 1**).

Outcome of Study

Effect on Sarcopenic Parameters (Muscle Mass, Muscle Strength, and Physical Performance)

The primary outcome of the study was to assess the impact of BCAA on muscle strength, muscle function, and muscle mass in the patients with LC. Concerning muscle strength, the hand-grip strength score was significantly ($p = 0.00$) improved (23.79 ± 5.28 kg) after treatment of 6 months in the BCAA arm (25.94 ± 5.14 kg) (**Figure 2A**). Furthermore, in terms of muscle function, gait speed score was significantly ($p = 0.00$) improved from before treatment (0.83 ± 0.07 m s^{-1}) to after treatment of 6 months (1.12 ± 0.04 m s^{-1}) (**Figure 2B**). For muscle mass, total abdominal muscle area (TAMA), fat fold triceps (FFT), and mid arm muscle circumference (MAMC) were statistically significant ($p = 0.001$), ($p = 0.039$), and ($p = 0.03$), respectively, in the BCAA group with the increased mean of 2.41 ± 0.27, 2.41 ± 0.25, and 2.80 ± 0.20, respectively (**Figures 2C–F**).

Effect on Cirrhotic Complications and Survival

Figure 3 depicts the cumulative event-free survival of the BCAA and ALB groups. There was no significant difference in time course event between the two groups on the basis of intention to treat (log-rank Mantel–Cox; $P = 0.600$). **Table 3** shows the incidence rates of major cirrhosis-related events in both the groups. The total cirrhotic-related complications occurred fewer in the BCAA group than in the L-ALB group [$P = 0.007$; odd ratio (OR): 0.823; 95% *CI*: 0.72–1.445]. In comparison to the ALB group, the progression and aggravation of hepatic encephalopathy were significantly lower in the BCAA group. There was no significant inter-category variation in the following complications: variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis, ascites formation, and hepatocellular carcinoma. The cumulative event-free survival was significantly better in the BCAA group 22.31 ± 0.56 weeks (95% $CI = 21.21–23.61$ weeks) than in the ALB-group: 21.11 ± 0.77 weeks (95% $CI = 19.59 ± 22.63$ weeks); $p = 0.00$ (**Figure 3**).

Outcomes on Laboratory Parameters

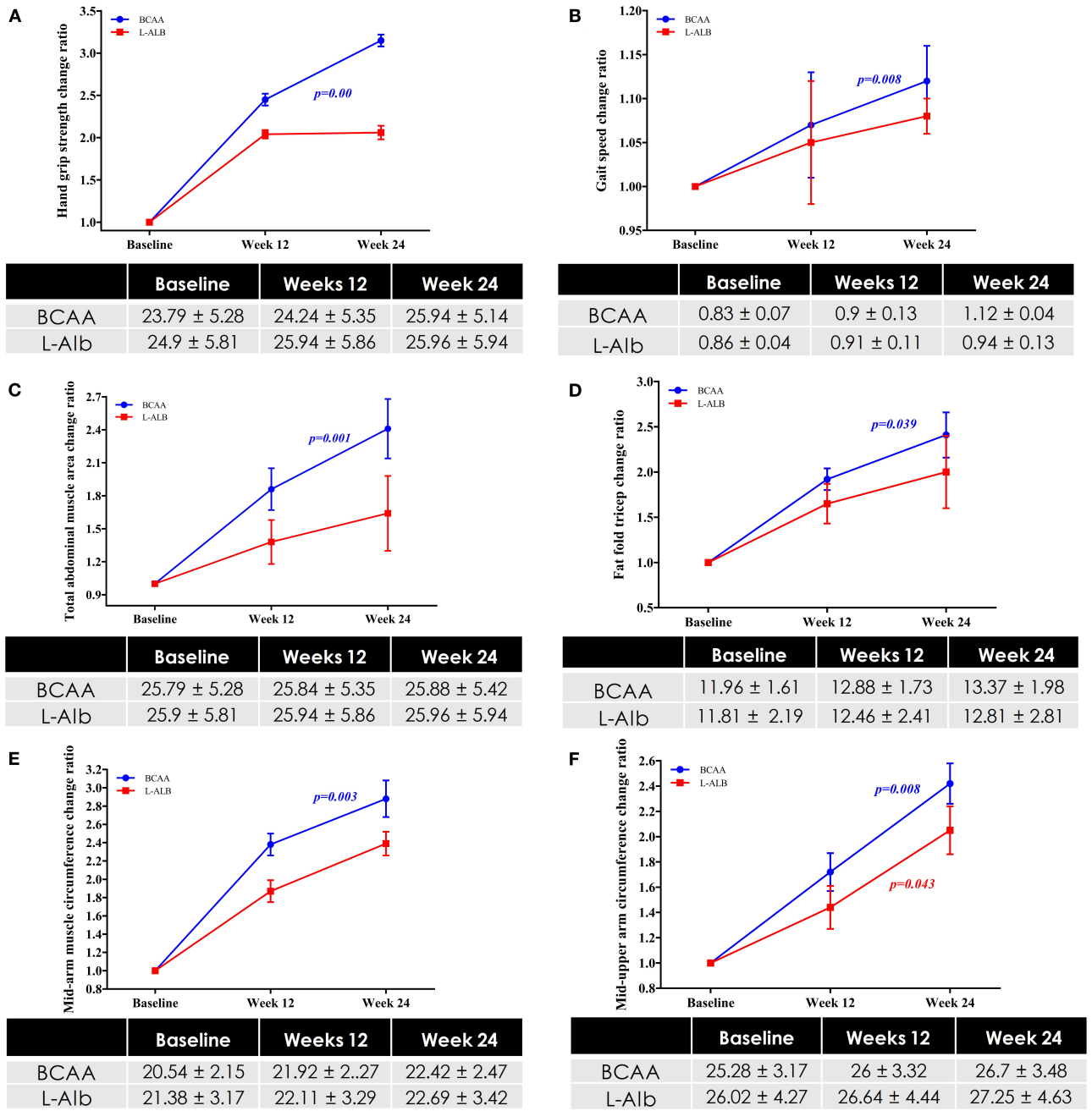
The changes in important laboratory markers over 24 weeks are compared between the two groups in **Figure 4**. The prevalence and severity CTP score (9.96 ± 2.80–8.06 ± 1.29) and bilirubin level (4.60 ± 1.81–3.33 ± 1.41) decreased and improved significantly in the BCAA group ($p = 0.020$ and $p = 0.016$), respectively (**Figures 4A,B**). However, there was no significant improvement in the subgroup analysis of serum albumin (**Figures 4A,C**). The MELD-score decreased significantly ($p = 0.001$) from 13.64 ± 2.61 to 16.34 ± 1.97 in the BCAA group overtime of 24 weeks.

Safety Profile and Product Compliance

During the study, the incidence of adverse events and adverse drug reactions were not reported in both the groups (data not shown). The given products were well-complaint among all the patients.

DISCUSSION

According to the best of our research, there is a scarcity of data on the involvement of BCAA in LC, primarily from the Asian subcontinent. Addressing the dearth of evidence, we account to report the first finding from India. This randomized clinical trial aimed to evaluate the potential benefits of nutritional



	Baseline	Weeks 12	Week 24
BCAA	23.79 ± 5.28	24.24 ± 5.35	25.94 ± 5.14
L-Alb	24.9 ± 5.81	25.94 ± 5.86	25.96 ± 5.94

	Baseline	Weeks 12	Week 24
BCAA	0.83 ± 0.07	0.9 ± 0.13	1.12 ± 0.04
L-Alb	0.86 ± 0.04	0.91 ± 0.11	0.94 ± 0.13

	Baseline	Weeks 12	Week 24
BCAA	25.79 ± 5.28	25.84 ± 5.35	25.88 ± 5.42
L-Alb	25.9 ± 5.81	25.94 ± 5.86	25.96 ± 5.94

	Baseline	Weeks 12	Week 24
BCAA	11.96 ± 1.61	12.88 ± 1.73	13.37 ± 1.98
L-Alb	11.81 ± 2.19	12.46 ± 2.41	12.81 ± 2.81

	Baseline	Weeks 12	Week 24
BCAA	20.54 ± 2.15	21.92 ± 2..27	22.42 ± 2.47
L-Alb	21.38 ± 3.17	22.11 ± 3.29	22.69 ± 3.42

	Baseline	Weeks 12	Week 24
BCAA	25.28 ± 3.17	26 ± 3.32	26.7 ± 3.48
L-Alb	26.02 ± 4.27	26.64 ± 4.44	27.25 ± 4.63

FIGURE 2 | (A) Changes in Hand-grip strength in BCAA and L-ALB group over a period of 24 weeks. **(B)** Changes in muscle function in BCAA and L-ALB group over a period of 24 weeks. Changes in muscle mass based on the different variables; **(C)** Total abdominal muscles area (TAMA) circumference; **(D)** Fat-fold triceps; **(E)** Mid-upper arm circumference; **(F)** Mid-arm muscle circumference in BCAA and L-ALB group over 24 weeks. Statistically significant at $p < 0.05$.

supplementation with BCAA in decompensated LC. This study results indicated that long-term BCAA supplementation, such as valine, leucine, and isoleucine, has beneficial effects on sarcopenia (muscle mass, muscle strength, and muscle function), with the decrease in the cirrhotic-related complications in several secondary outcomes (CTP score, albumin, and MELD).

In the present study, sarcopenia, as assessed on variables of muscle mass, muscle strength, and muscle function consistent with the updated EWGSOP2, 2018, has improved significantly with BCAA supplementation. One of the key pathophysiologic mechanisms underlying this spectacle is the increase of muscle protein due to mammalian target of rapamycin (mTOR) activation and reduced muscle protein degradation (24, 25).

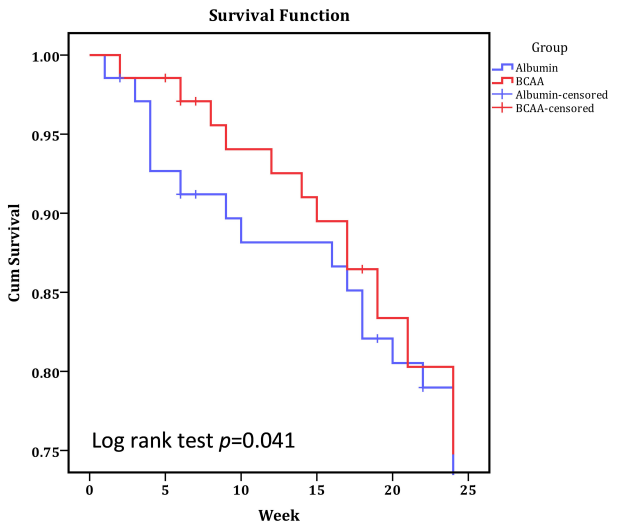


FIGURE 3 | Kaplan Meier analysis of cumulative event-free survival in patients supplemented with BCAA and L-ALB group over 24 weeks. Events were considered death (any reason) and deterioration to exclusion criteria. Statistically significant at $p < 0.05$.

TABLE 3 | Incidence of major cirrhosis related events in BCAA and L-ALB group.

Events	BCAA group	L-ALB group	*p*-value*
Number of patients	52	54	-
Loss of follow-up	3 (2.2)	2 (1.4)	0.649
Death	4 (2.9)	5 (3.6)	0.730
Non-compliance	4 (2.9)	3 (2.2)	0.698
Variceal hemorrhage	1 (0.7)	2 (1.4)	0.559
Hepatic Encephalopathy (III Grade)	11 (10.9)	14 (13.0)	0.031
Hepatorenal syndrome	1 (0.7)	1 (0.7)	1.000
Spontaneous bacterial peritonitis	1 (0.7)	2 (1.4)	0.589
Aggravations of ascites	2 (1.4)	3 (2.2)	0.649
Development of hepatocellular carcinoma	1 (0.7)	1 (0.7)	1.000

**Statistically significant at $p < 0.05$.*

BCAA has a better efficacious energy substrate utilization in contrast to that of glucose and fatty acids. BCAA breakdown primarily takes place in the peripheral tissues (muscles, brain, and adipose tissue), extra-hepatically, so even if the hepatocytes are damaged and incapable of synthesizing protein in the liver, BCAA (especially leucine) in the muscles would promote protein synthesis, as concluded from the previous studies (1, 23, 26). Foremost, cirrhosis-related event, the hepatic encephalopathy, occurred less frequently in the BCAA group than in the ALB group. Early clinical trials have shown the effectiveness of BCAA supplementation on patients with malnutrition and hepatic encephalopathy (27, 28). The metabolism of amino acids is related to the progression of chronic liver disease, resulting in a lower circulating BCAA/aromatic-amino-acid ratio (29, 30). Due to the elevated ammonia levels in the serum and brain, this change can cause hepatic encephalopathy. While there is evidence of the beneficial function of BCAAs in hepatic encephalopathy, there is also contradictory data (30). During oral BCAA supplementation, the EFS improved, such as death from any cause and worsening of liver disease with or without the production of HCC, nonetheless, significant improvement can be better appreciated in a further long-term study (11). The current guidelines of the European Society for Clinical Nutrition and Metabolism recommend taking a BCAA-enriched formula in case of hepatic encephalopathy during enteral nutrition (31).

Other secondary outcomes have improved. The patients supplemented with BCAA exhibited significant improvement in MELD score over time. A Korean, retrospective, observational cohort study showed similar improvement in MELD score, which is a well-known predictive indicator of the pre-transplant waiting list death rate (32–34). However, the advancement of liver disease and progression of MELD score can be slowed by antiviral agents, such as nucleos(t)ide analogs and abstaining alcohol consumption in the existing study. Additionally, nutritional support is known to be an independent factor for improving these outcomes in these patients (32). Interestingly, we found decreased serum bilirubin levels which may potentially be responsible for the lower MELD score in the BCAA group. The results are influenced by the progressive exclusion of subjects who reached the event threshold because ANOVA takes the time course of parameters of subjects that completed the study in all treatment groups. These results are similar to an Italian randomized prospective study that also reports improvement in bilirubin level and CTP scores (11).

Significant related changes in CTP scores were consistent with the Korean study (32, 35). The changing aspects of the CTP hold greater dynamics in comparison to serum bilirubin level in various conditions, such as prediction of mortality in patients with cirrhosis. The improvement in the serum albumin levels in the present study can contribute to the increase in the total intake of proteins and the anti-catabolic effects of BCAA. In line with the preceding findings, an *in-vitro* study reports that, among three amino acids in BCAA, leucine plays a role in protein synthesis, which ultimately increases the synthesis and secretion of albumin by the hepatocytes (36, 37). BCAA has also been shown to improve albumin turnover (6) in cirrhotics, thus improving the net protein catabolism and serum albumin levels (38, 39). As a result, changes in the albumin levels can be attributed to comprehensive changes in CTP scores; nevertheless, a substantial quantity of evidence is required to validate the changes in scores. Even though biased by several aspects (40), CTP scores can predict prognosis, and its serial determinations can further improve its diagnostic accuracy in patients with cirrhosis (41–43). This finding is consistent with the findings of earlier randomized controlled trials, in which BCAA supplementation resulted in a significant improvement in the CTP score when compared with L-ABL and maltodextrins (11, 44).

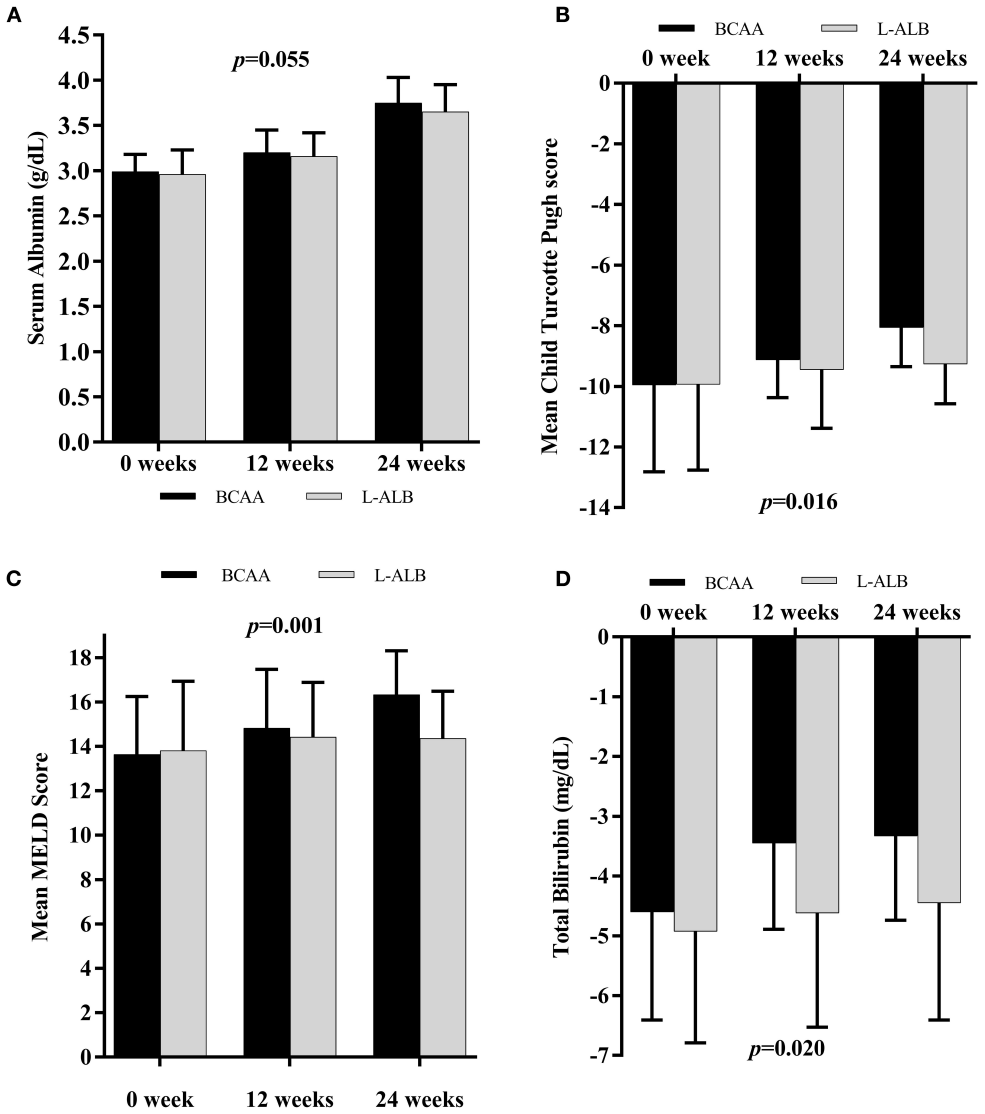


FIGURE 4 | Mean changes in Albumin concentration **(A)**, Child Turcotte Pugh score **(B)**, MELD score **(C)**, and Total Bilirubin level **(D)** in subjects supplemented with BCAA (black scale) or L-ALB (grayscale) over 24 weeks. MELD, Model for End-stage Liver Disease. Statistically significant at $p < 0.05$.

In the present study, seven patients were withdrawn, either due to non-compliance or loss of follow-up in the BCAA group. However, even though the dietician provided adequate nutritional guidance, four patients withdrew from the study due to poor-palatability with the BCAA supplementation. The previous studies have reported non-compliance that was mainly attributed due to bitter taste, which leads to low palatability of supplements (35). Adverse effects, mostly gastrointestinal symptoms, have also been reported as a reason behind non-compliance, though no such reasons for non-compliance were reported in the present study. Poor medication compliance indeed affects the clinical effects. Hence, the pharmaceutical company needs to enhance the formulation to increase compliance.

However, there were some limitations of the study. First, the major problem was the large number of subjects who withdrew from the study, either because of non-compliance or lost follow-up. Therefore, there is a requirement for new and more palatable formulations to improve compliance. Second, further research for an optimal period with indication of BCAA supplementation should be conducted, taking into account hepatic inflammatory biomarkers, degree of malnutrition, and also to elucidate changes on the physical activity and nutritional intake would be needed to improve clinical outcomes.

CONCLUSIONS

Long-term oral BCAA supplementation improved significant sarcopenic indicators, such as muscular strength, muscle

function, muscle mass, and prognostic markers in patients with advanced LC, according to this study. Treatment with BCAA results in oral BCAA supplementation reduced cirrhosis-related complications, especially the development or worsening of hepatic encephalopathy, though further long-term follow-up is required to assess in-depth event-free survival. As a result, long-term oral BCAA supplementation can improve the clinical condition of patients with advanced liver disease.

DATA AVAILABILITY STATEMENT

The data generated and/or analyzed in the BCAAS study are for academic purposes and are available on appropriate requests from the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nims University Rajasthan Jaipur Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS: conceptualization, investigation, validation, and writing—original draft. AM: methodology and project administration. DN: conceptualization, validation, resources, writing—original draft, supervision, and funding. RR: conceptualization, writing, reviewing, editing, supervision, and funding. PS: investigation, validation, and writing—original draft. PR: investigation, formal analysis, and writing—original draft. SS: investigation, formal analysis, writing, reviewing, and editing. PM and SA: investigation, writing, reviewing, and editing. BT: conceptualization, resources, writing, reviewing, editing, supervision, and funding. All authors contributed to the article and approved the submitted version.

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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.2021.715795/full#supplementary-material

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Combination of Albumin-Globulin Score and Sarcopenia to Predict Prognosis in Patients With Renal Cell Carcinoma Undergoing Laparoscopic Nephrectomy

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We conducted a multicenter clinical study to construct a novel index based on a combination of albumin-globulin score and sarcopenia (CAS) that can comprehensively reflect patients' nutritional and inflammatory status and assess the prognostic value of CAS in renal cell carcinoma (RCC) patients. Between 2014 and 2019, 443 patients from 3 centers who underwent nephrectomy were collected (343 in the training set and 100 in the test set). Kaplan-Meier curves were employed to analyze the impact of albumin-globulin ratio (AGR), albumin-globulin score (AGS), sarcopenia, and CAS on overall survival (OS) and cancer-specific survival (CSS) in RCC patients. Receiver operating characteristic (ROC) curves were used to assess the predictive ability of AGR, AGS, sarcopenia, and CAS on prognosis. High AGR, low AGS, and nonsarcopenia were associated with higher OS and CSS. According to CAS, the training set included 60 (17.5%) patients in grade 1, 176 (51.3%) patients in grade 2, and 107 (31.2%) patients in grade 3. Lower CAS was linked to longer OS and CSS. Multivariate Cox regression analysis revealed that CAS was an independent risk factor for OS (grade 1 vs. grade 3: aHR = 0.08; 95% CI: 0.01–0.58, $p = 0.012$; grade 2 vs. grade 3: aHR = 0.47; 95% CI: 0.25–0.88, $p = 0.018$) and CSS (grade 1 vs. grade 3: aHR = 0.12; 95% CI: 0.02–0.94, $p = 0.043$; grade 2 vs. grade 3: aHR = 0.31; 95% CI: 0.13–0.71, $p = 0.006$) in RCC patients undergoing nephrectomy. Additionally, CAS had higher accuracy in predicting OS (AUC = 0.687) and CSS (AUC = 0.710) than AGR, AGS, and sarcopenia. In addition, similar results were obtained in the test set. The novel index CAS developed in this study, which reflects patients' nutritional and inflammatory status, can better predict the prognosis of RCC patients.

Keywords: renal cell carcinoma, combination of albumin-globulin score, sarcopenia, albumin-globulin score, sarcopenia, prognostic indicator, nephrectomy

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INTRODUCTION

Renal cell carcinoma (RCC), alternatively referred to as renal cancer, is 1 of the most prevalent malignancies of the urinary system. It is common cancer with morbidity of 2–3% in systemic malignant tumors and 80–85% in renal cancers (1). Due to its increasing incidence, 170,000 RCC patients died worldwide in 2018, with a mortality rate of ∼ 2.7% (2). When RCC is early detected, it can be effectively treated with radical or partial nephrectomy, with a 5-year survival rate of 93% (3). However, over 30% of patients progress to advanced RCC at the first diagnosis, and 10–20% of patients with early RCC experience recurrence after treatments (4). Advanced RCC patients have a decreased 5-year survival rate of 67% due to regional and distant metastases (5).

Apart from the time of diagnosis, numerous other factors affect the prognosis of RCC patients, such as tumor size, pathological stage, and other biochemical indicators (6). Albumin (ALB) and globulin (GLB) are indicators of systemic nutritional status, and their ratio (AGR) is an independent prognostic factor for RCC patients (7). Albumin-globulin score (AGS) is another model based on ALB and GLB (8). However, no previous studies have investigated the relationship between AGR and AGS and long-term outcomes in RCC patients undergoing nephrectomy.

Sarcopenia is an emerging index of nutritious status, an extensive and progressive skeletal muscle disease characterized by loss of muscle mass and strength (9). Sarcopenia was assessed by measuring lumbar skeletal muscle index (SMI) and total psoas index (TPI) preoperatively using computed tomography (CT). Recently, sarcopenia was reported to be connected to inflammatory diseases, malignancies, and malnutrition (10). Sarcopenia, in particular, is a poor prognostic indicator in various tumors, including hepatocellular carcinoma, gastroesophageal tumor, colorectal cancer, and urothelial carcinomas (11), and our previous study found that sarcopenia is a risk factor for the survival time of cancer patients, including RCC and bladder cancer (12, 13).

This study aimed to determine the influence of AGR, AGS, and sarcopenia on the prognosis of RCC patients treated with laparoscopic nephrectomy and to build a novel index based on a combination of AGS and sarcopenia (CAS) that can more comprehensively reflect the nutritional and inflammatory status of RCC patients and investigate the prognostic ability of CAS in RCC patients undergoing laparoscopic nephrectomy.

MATERIALS AND METHODS

Study Design and Patients

This multicenter research retrospectively collected clinical data from 590 RCC patients who underwent partial or radical nephrectomy at Zhongda Hospital Southeast University, Shanghai Tenth People's Hospital, and Shidong Hospital from January 2014 to December 2019. The inclusion criteria were set as follows: patients with pathologically diagnosed RCC; and patients who received surgical treatment with therapeutic purposes for the first time. The exclusion criteria were set as follows: patients who received other anticancer treatment before nephrectomy, such as transcatheter arterial chemoembolization, radiofrequency ablation, or chemotherapy; patients with other malignant tumors; and patients without complete medical records or lost to follow-up. After screening, this study finally included 443 patients.

A total of 343 patients from Zhongda Hospital Southeast University were included as the training set, and 100 patients from Shanghai Tenth People's Hospital and Shidong Hospital were adopted to the test set. All included patients have signed written informed consent. The methodology of this study followed the criteria outlined in Declaration of Helsinki (as revised in 2013) and was ethically approved by Ethics Committees and Institutional Review Boards of all participating institutions.

Clinical Data Collection and Follow-Up

Baseline information, laboratory examination, and imaging findings of all patients were reviewed and retrieved from hospital electronic medical records. The collected basic characteristics of patients include age, gender, body mass index [BMI, calculated by weight (kg)/height^2 (m^2)], hypertension, diabetes, cardiovascular disease, smoking, surgery type, hemoglobin, ALB, GLB, AGR, AGS, SMI, platelets, neutrophils, lymphocytes, and survival time. Tumor-related clinic pathological features were also collected, including laterality, AJCC stage, TNM stage, and Fuhrman grade. All included patients were followed up to December 2020 by telephone every 3 months. The laboratory test data were measured 2 days before surgery or closest to the time of surgery. Neutrophil to lymphocyte ratio (NLR) is the ratio of neutrophils to lymphocytes, whereas platelet to lymphocyte ratio (PLR) is the ratio of platelets to lymphocytes. AGR is the ratio of serum ALB to GLB. According to previous studies, AGS = 0 means ALB > 41.7 g/L and GLB < 28.6 g/L, AGS = 2 means ALB < 41.7 g/L and GLB > 28.6 g/L, and AGS = 1 for the remaining patients (8). The diagnosis of sarcopenia was determined based on previous studies (12). CAS was defined as follows: patients with low AGS (AGS = 0) and non-sarcopenia were included in CAS grade 1, patients with high AGS (AGS = 1/2) and sarcopenia were included in CAS grade 3, and the remaining patients were included in CAS grade 2. Overall survival (OS) was calculated from the surgical treatment date to death date or the last follow-up. Cancer-specific survival (CSS) was calculated from the date of therapeutic resection to the date of death due to RCC.

Statistical Analysis

Continuous data are presented as mean ± standard deviation (SD) and categorical data as number (%). Categorical variables were analyzed using chi-square test or Fisher's exact tests and continuous variables were analyzed using *t*-test. AGR was determined using receiver operating characteristic (ROC) curves and patients were divided into AGR > 1.33 and AGR ≤ 1.33 groups according to AGR levels. Patients with AGS = 0 were included in the low AGS group, and those with AGS = 1 or 2 were included in the high AGS group. We divided patients into sarcopenia and non-sarcopenia groups according to SMI.

Kaplan-Meier curves were employed to assess the effects of AGR, AGS, SMI, and CAS on OS and CSS. ROC curves were

TABLE 1 | Baseline characteristics of patients in the training and test sets.

Characteristic	All Patients	Training Set	Test Set	*P*-value
	No. (%)	No. (%)	No. (%)	
Total patients	443	343	100	
Age, y, mean (SD)	58.02 (12.44)	57.47 (12.56)	59.90 (11.89)	0.086
Age categorized, y				0.027
≤65	318 (71.8)	255 (74.3)	63 (63.0)	
>65	125 (28.2)	88 (25.7)	37 (37.0)	
Gender				0.442
Male	296 (66.8)	226 (65.9)	70 (70.0)	
Female	147 (33.2)	117 (34.1)	30 (30.0)	
BMI, kg/m^2, mean (SD)	24.60 (3.55)	24.69 (3.62)	24.30 (3.29)	0.330
BMI categorized, kg/m^2				0.032
<25	251 (56.7)	185 (53.9)	66 (66.0)	
≥25	192 (43.3)	158 (46.1)	34 (34.0)	
Hypertension				0.444
No	251 (56.7)	191 (55.7)	60 (60.0)	
Yes	192 (43.3)	152 (44.3)	40 (40.0)	
Diabetes				0.993
No	372 (84.0)	288 (84.0)	84 (84.0)	
Yes	71 (16.0)	55 (16.0)	16 (16.0)	
Cardiovascular diseases				0.211
No	392 (88.5)	300 (87.5)	92 (92.0)	
Yes	51 (11.5)	43 (12.5)	8 (8.0)	
Smoking				0.883
No	370 (83.5)	286 (83.4)	84 (84.0)	
Yes	73 (16.5)	57 (16.6)	16 (16.0)	
Surgery type				<0.001
Partial nephrectomy	268 (60.5)	187 (54.5)	81 (81.0)	
Radical nephrectomy	175 (39.5)	156 (45.5)	19 (19.0)	
Laterality				0.580
Left	224 (50.6)	171 (49.9)	53 (53.0)	
Right	219 (49.4)	172 (50.1)	47 (47.0)	
AJCC stage				0.200
I	329 (74.3)	256 (74.6)	73 (73.0)	
II	26 (5.9)	19 (5.5)	7 (7.0)	
III	60 (13.5)	45 (13.1)	15 (15.0)	
IV	28 (6.3)	23 (6.7)	5 (5.0)	
T-stage				1.000
T1	336 (75.8)	260 (75.8)	76 (76.0)	
T2	30 (6.8)	23 (6.7)	7 (7.0)	
T3	66 (14.9)	51 (14.9)	15 (15.0)	
T4	11 (2.5)	9 (2.6)	2 (2.0)	
N-stage				0.590
N0	425 (95.9)	330 (96.2)	95 (95.0)	
N1	18 (4.1)	13 (3.8)	5 (5.0)	
M-stage				0.585
M0	424 (95.7)	327 (95.3)	97 (97.0)	
M1	19 (4.3)	16 (4.7)	3 (3.0)	
Fuhrman grade				0.915
I	74 (16.7)	55 (16.0)	19 (19.0)	
II	276 (62.3)	216 (63.0)	60 (60.0)	
III	83 (18.7)	64 (18.7)	19 (19.0)	
IV	10 (2.3)	8 (2.3)	2 (2.0)	
Hemoglobin (g/L), mean (SD)	133.41 (19.98)	133.14 (20.34)	134.39 (18.77)	0.585
ALB, [g/L, mean (SD)]	41.55 (4.71)	41.12 (4.88)	43.06 (3.74)	<0.001
GLB, [U/L, mean (SD)]	28.40 (5.58)	28.82 (5.72)	26.94 (4.79)	0.003
AGR [mean, (SD)]	1.52 (0.33)	1.48 (0.34)	1.64 (0.27)	<0.001
AGS				0.005
Low (0)	120 (27.1)	82 (23.9)	38 (38.0)	
High (1/2)	323 (72.9)	261 (76.1)	62 (62.0)	
SMI, cm^2/m^2, mean (SD)				0.126
Non-sarcopenic	286 (64.6)	215 (62.7)	71 (71.0)	
Sarcopenic	157 (35.4)	128 (37.3)	29 (29.0)	
Survival time (months)	32.88 (19.52)	32.63 (18.90)	33.71 (21.58)	0.628

Continuous data are presented as the mean ± standard deviation and categorical data as n (%).

For categorical variables, P-values were analyzed by chi-square tests. For continuous variables, the t-test for slope was used in generalized linear models. For T-stage, M-stage, and Fuhrman grade, Fisher's exact test was used.

SD, standard deviation; BMI, Body mass index; AJCC, American Joint Committee on Cancer; ALB, albumin; GLB, globulin; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index.

utilized to compare the predictive ability of AGR, AGS, SMI, NLR, PLR and CAS on OS and CSS and were numerated using the area under the curve (AUC). Univariate and multivariate Cox regression models were deployed to assess the relationship between CAS and OS and CSS. In multivariate Cox regression analysis, we constructed three models to assess the relationship between CAS and OS and CSS separately and calculated the associated adjusted hazard ratios (aHR) and 95% confidence intervals (CI). In the basic model, we adjusted for age, gender, BMI, hypertension, diabetes, cardiovascular diseases, and smoking. In the core model, we added surgical type and laterality to the seven variables in the base model. In the extended model, we added six variables of AJCC stage, T stage, N stage, M stage, and Fuhrman grade based on the core model. Statistical analysis of this research was performed using SPSS software (version 26.0) and Graphpad Prism (version 8.3.0). A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

The clinic pathological characteristics of 443 patients included in this study are presented in **Table 1**. In the entire cohort, the mean age of all patients was 58.02 years, their BMI was 24.60 kg/m^2, and their survival time was 32.88 months. Preoperative ALB, GLB, AGR, BMI, and SMI levels in surviving patients were higher than those in dead patients (**Figure 1**). In training and test sets, we found that most patients were male, age <65 years, BMI <25 kg/m^2, without hypertension or diabetes, or cardiovascular disease. The common tumor types were AJCC I

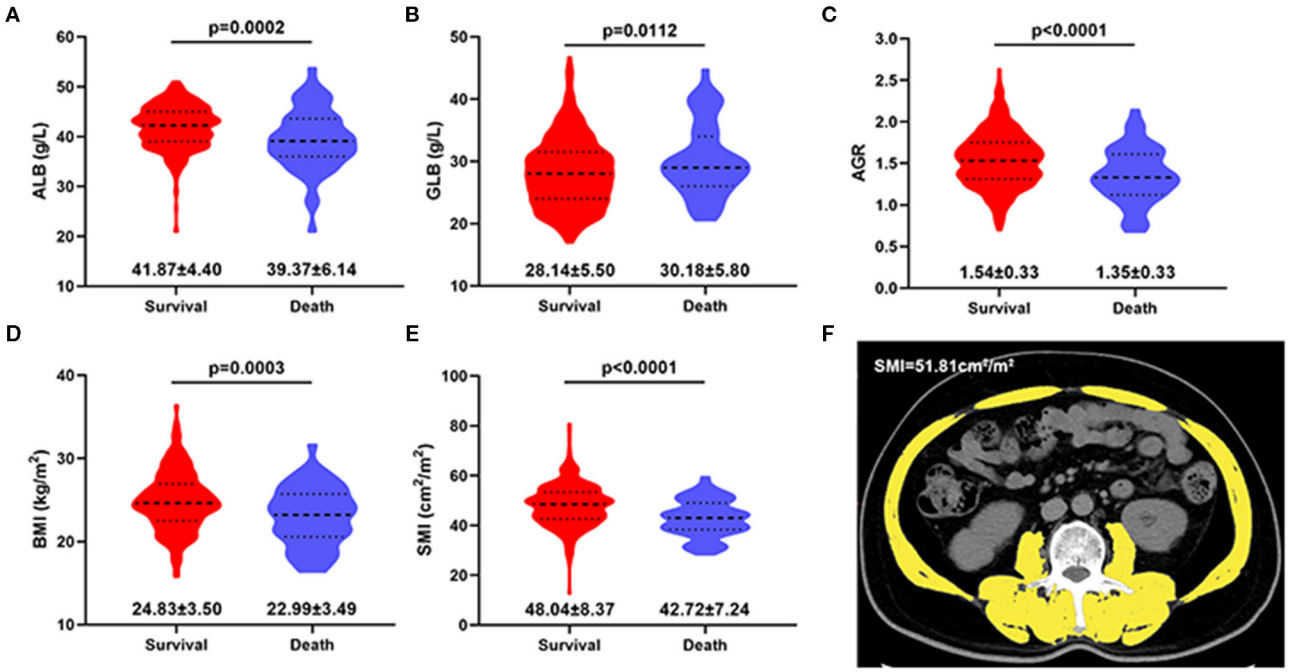

FIGURE 1 | Violin plots showing the preoperative ALB **(A)**, GLB **(B)**, AGR **(C)**, BMI **(D)** and SMI **(E)** level in survival and death group at the end of follow-up. **(F)** Axial CT images of the third lumbar region were used to measure the skeletal muscle index (yellow area). ALB, albumin; GLB, globulin; AGR, albumin to globulin ratio; BMI, Body mass index; SMI, skeletal muscle index. Data are presented as the mean ± standard deviation.

stage, T1 stage, N0 stage, M0 stage, and Fuhrman II grade. In addition, no statistically difference was observed in survival time between patients in training and test sets.

As indicated in **Table 2**, in the training set, 82 (23.9%) patients were classified into low AGS group and 261 (76.1%) patients into high AGS (AGS = 1/2) group according to AGS, while 215 (62.7%) patients had non-sarcopenia and 128 (37.3%) patients had sarcopenia assessed by SMI. Kaplan-Meier survival curves indicated that high AGR, low AGS, and non-sarcopenia predicted higher overall survival (OS) and cancer-specific survival (CSS) in both training and test sets (**Figure 2** and **Supplementary Figure 1**). There was an increased proportion of patients aged >65 years, BMI < 25 kg/m^2 in high AGS group or sarcopenia group. In addition, other variables, such as surgical type, hemoglobin, ALB, GLB, and AGR, were comparable between low and high AGS or sarcopenia and non-sarcopenia groups.

When stratified by CAS grade, 60 (17.5%) patients were CAS grade 1, 176 (51.3%) patients were CAS grade 2, and 107 (31.2%) patients were CAS grade 3. **Table 3** displays the relationship between CAS and patient clinicopathology. We found that CAS grade 3 group had a higher percentage of age >65 years, female, BMI <25 kg/m^2, AJCC III/IV stage, T3–4 stage, N1 stage, M1 stage, and Fuhrman III/IV grade than those in the other two groups. In training and test sets, survival time progressively decreased with increasing CAS grade, and patients with CAS grade 3 were associated with the lowest OS and CSS (**Figure 3** and **Supplementary Figure 2**). In addition, statistical differences existed among the three groups in age, BMI, surgical type, hemoglobin, ALB, GLB, and AGR variables.

In addition, we constructed three multivariate Cox regression models to assess the correlation of CAS with OS and CSS (**Table 4**). The results revealed that CAS was consistently an independent risk factor for OS (extended model: CAS grade 1 vs. CAS grade 3: aHR = 0.08; 95% CI: 0.01–0.58, $p = 0.012$; CAS grade 2 vs. CAS grade 3: aHR = 0.47; 95% CI: 0.25–0.88, $p = 0.018$) and CSS (extended model: CAS grade 1 vs. CAS grade 3: aHR = 0.12; 95% CI: 0.02-0.94, $p = 0.043$; CAS grade 2 vs. CAS grade 3: aHR = 0.31; 95% CI: 0.13–0.71, $p = 0.006$), whether in the basic, core, or extended models and CAS grade 3 was associated with the worst prognosis.

Receiver operating characteristic (ROC) curves were utilized to evaluate the prognostic ability of AGR, AGS, SMI, NLR, PLR, and CAS in RCC patients undergoing laparoscopic nephrectomy (**Table 5**). We discovered that CAS had higher predictive power for OS (training set: AUC = 0.687, 95% CI: 0.607–0.766, $p < 0.001$; test set: AUC = 0.724, 95% CI: 0.557–0.891, $p = 0.012$) and CSS (training set: AUC = 0.710, 95% CI: 0.613–0.808, $p < 0.001$; test set: AUC = 0.805, 95% CI: 0.648–0.962, $p = 0.004$) than the other five indicators in training and test sets (**Figure 4** and **Supplementary Figure 3**).

DISCUSSION

In the current study, given the prognostic value of ALB, GLB, and sarcopenia in RCC patients, we combined them to

TABLE 2 | Comparison between AGS, SMI and clinic pathological characteristics in training set.

Characteristic	AGS		*P*-value	SMI		*P*-value
	Low (0)	High (1/2)		Non-sarcopenic	Sarcopenic	
	No. (%)	No. (%)		No. (%)	No. (%)	
Total patients	82	261		215	128	
Age, y, mean (SD)	53.00 (12.79)	58.87 (12.18)	<0.001	55.73 (11.72)	60.40 (13.40)	0.001
Age categorized, y			0.041			<0.001
≤65	68 (82.9)	187 (71.6)		175 (81.4)	80 (62.5)	
>65	14 (17.1)	74 (28.4)		40 (18.6)	48 (37.5)	
Gender			0.289			0.209
Male	58 (70.7)	168 (64.4)		147 (68.4)	79 (61.7)	
Female	24 (29.3)	93 (35.6)		68 (31.6)	49 (38.3)	
BMI, kg/m^2, mean (SD)	25.07 (3.68)	24.57 (3.60)	0.271	25.38 (3.42)	23.53 (3.66)	<0.001
BMI categorized, kg/m^2			0.184			0.660
<25	39 (47.6)	146 (55.9)		114 (53.0)	71 (55.5)	
≥25	43 (52.4)	115 (44.1)		101 (47.0)	57 (44.5)	
Hypertension			0.551			0.198
No	48 (58.5)	143 (54.8)		114 (53.0)	77 (60.2)	
Yes	34 (41.5)	118 (45.2)		101 (47.0)	51 (39.8)	
Diabetes			0.769			0.442
No	68 (82.9)	220 (84.3)		178 (82.8)	110 (85.9)	
Yes	14 (17.1)	41 (15.7)		37 (17.2)	18 (14.1)	
Cardiovascular diseases			0.383			0.319
No	74 (90.2)	226 (86.6)		191 (88.8)	109 (85.2)	
Yes	8 (9.8)	35 (13.4)		24 (11.2)	19 (14.8)	
Smoking			0.831			0.604
No	69 (84.1)	217 (83.1)		181 (84.2)	105 (82.0)	
Yes	13 (15.9)	44 (16.9)		34 (15.8)	23 (18.0)	
Surgery type			0.018			0.002
Partial nephrectomy	54 (65.9)	133 (51.0)		131 (60.9)	56 (43.8)	
Radical nephrectomy	28 (34.1)	128 (49.0)		84 (39.1)	72 (56.2)	
Laterality			0.217			0.282
Left	46 (56.1)	126 (48.3)		103 (47.9)	69 (53.9)	
Right	36 (43.9)	135 (51.7)		112 (52.1)	59 (46.1)	
AJCC stage			0.484			0.749
I	67 (81.7)	189 (72.4)		163 (75.8)	93 (72.7)	
II	3 (3.7)	16 (6.1)		13 (6.0)	6 (4.7)	
III	8 (9.8)	37 (14.2)		26 (12.1)	19 (14.8)	
IV	4 (4.9)	19 (7.3)		13 (6.0)	10 (7.8)	
T-stage			0.334			0.530
T1	67 (81.7)	193 (73.9)		166 (77.2)	94 (73.4)	
T2	4 (4.9)	19 (7.3)		16 (7.4)	7 (5.5)	
T3	8 (9.8)	43 (16.5)		28 (13.0)	23 (18.0)	
T4	3 (3.7)	6 (2.3)		5 (2.3)	4 (3.1)	
N-stage			0.316			0.774
N0	81 (98.8)	249 (95.4)		206 (95.8)	124 (96.9)	
N1	1 (1.2)	12 (4.6)		9 (4.2)	4 (3.1)	
M-stage			0.376			0.604
M0	80 (97.6)	247 (94.6)		206 (95.8)	121 (94.5)	
M1	2 (2.4)	14 (5.4)		9 (4.2)	7 (5.5)	

(Continued)

TABLE 2 | Continued

Characteristic	AGS		*P*-value	SMI		*P*-value
	Low (0)	High (1/2)		Non-sarcopenic	Sarcopenic	
	No. (%)	No. (%)		No. (%)	No. (%)	
Fuhrman grade			0.437			0.708
I	15 (18.3)	40 (15.3)		38 (17.7)	17 (13.3)	
II	53 (64.6)	163 (62.5)		134 (62.3)	82 (64.1)	
III	14 (17.1)	50 (19.2)		38 (17.7)	26 (20.3)	
IV	0 (0.0)	8 (3.1)		5 (2.3)	3 (2.3)	
Hemoglobin (g/L), mean (SD)	140.46 (16.10)	130.84 (21.00)	<0.001	135.40 (18.60)	129.33 (22.52)	0.007
ALB, [g/L, mean (SD)]	44.79 (2.22)	39.93 (5.08)	<0.001	41.57 (4.97)	40.29 (4.99)	0.022
GLB, [U/L, mean (SD)]	24.35 (2.85)	30.22 (5.68)	<0.001	28.75 (5.72)	28.93 (5.73)	0.782
AGR [mean, (SD)]	1.87 (0.25)	1.36 (0.28)	<0.001	1.50 (0.34)	1.45 (0.35)	0.186
Survival time (months)	35.48 (19.44)	31.74 (18.68)	0.119	32.84 (19.50)	32.28 (17.92)	0.791

Continuous data are presented as the mean ± standard deviation and categorical data as n (%).
For categorical variables, P-values were analyzed by chi-square tests. For continuous variables, the t-test for slope was used in generalized linear models. For AJCC stage, T-stage, N-stage, M-stage, and Fuhrman grade, Fisher's exact test was used.
SD, standard deviation; BMI, Body mass index; AJCC, American Joint Committee on Cancer; ALB, albumin; GLB, globulin; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index.

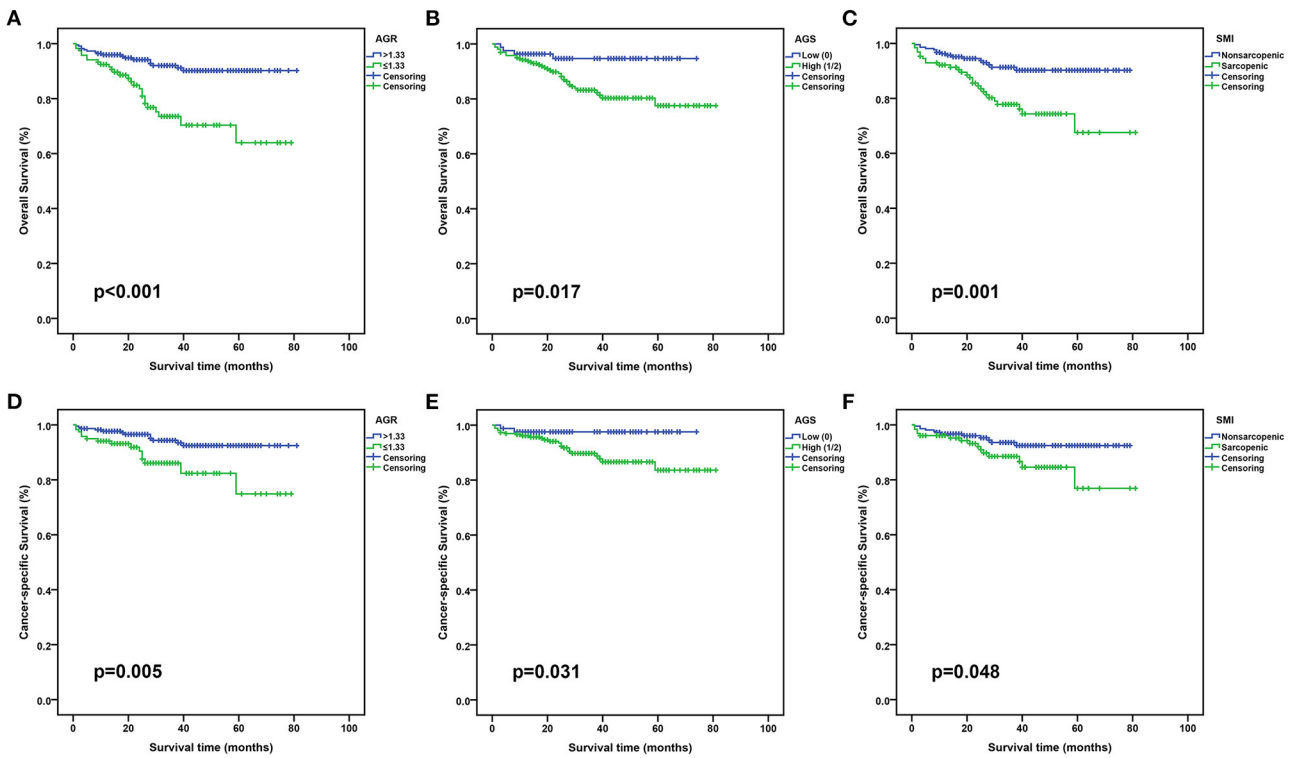

FIGURE 2 | Kaplan-Meier curves for OS and CSS stratified by AGR, AGS and SMI in the training set. **(A,D)**, AGR OS and CSS; **(B,E)**, AGS OS and CSS; **(C,F)**, SMI OS and CSS. OS, overall survival; CSS, cancer-specific survival; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index.

construct a new index (CAS), providing a more comprehensive response to systemic nutritional and inflammatory status. CAS has been demonstrated to have a predictive role in patients with intrahepatic cholangiocarcinoma (ICC). By retrospectively analyzing clinical data from 613 ICC patients, Li et al. (14) found that CAS was strongly associated with long-term postoperative outcomes for surgically treated ICC patients. We conducted a multicenter study to investigate the impact of CAS on the

TABLE 3 | Comparison between CAS and clinic pathological characteristics in training set.

Characteristic	CAS			*P*-value
	Grade 1	Grade 2	Grade 3	
	No. (%)	No. (%)	No. (%)	
Total patients	60 (17.5)	176 (51.3)	107 (31.2)	
Age, y, mean (SD)	51.23 (12.56)	57.52 (11.05)	60.89 (13.63)	<0.001
Age categorized, y				<0.001
≤65	50 (83.3)	141 (80.1)	64 (59.8)	
>65	10 (16.7)	35 (19.9)	43 (40.2)	
Gender				0.180
Male	42 (70.0)	121 (68.8)	63 (58.9)	
Female	18 (30.0)	55 (31.2)	44 (41.1)	
BMI, kg/m^2, mean (SD)	25.72 (3.51)	25.05 (3.45)	23.52 (3.68)	<0.001
BMI categorized, kg/m^2				0.310
<25	27 (45.0)	98 (55.7)	60 (56.1)	
≥25	33 (55.0)	78 (44.3)	47 (43.9)	
Hypertension				0.946
No	33 (55.0)	97 (55.1)	61 (57.0)	
Yes	27 (45.0)	79 (44.9)	46 (43.0)	
Diabetes				0.430
No	48 (80.0)	152 (86.4)	88 (82.2)	
Yes	12 (20.0)	24 (13.6)	19 (17.8)	
Cardiovascular diseases				0.261
No	53 (88.3)	158(89.8)	89 (83.2)	
Yes	7 (11.7)	18 (10.2)	18 (16.8)	
Smoking				0.742
No	52 (86.7)	145 (82.4)	89 (83.2)	
Yes	8 (13.3)	31 (17.6)	18 (16.8)	
Surgery type				<0.001
Partial nephrectomy	45 (75.0)	96 (54.5)	46 (43.0)	
Radical nephrectomy	15 (25.0)	80 (45.5)	61 (57.0)	
Laterality				0.834
Left	32 (53.3)	86 (48.9)	54 (50.5)	
Right	28 (46.7)	90 (51.1)	53 (49.5)	
AJCC stage				0.237
I	49 (81.7)	134 (76.1)	73 (68.2)	
II	2 (3.3)	11 (6.2)	6 (5.6)	
III	5 (8.3)	24 (13.6)	16 (15.0)	
IV	4 (6.7)	7 (4.0)	12 (11.2)	
T-stage				0.155
T1	49 (81.7)	137 (77.8)	74 (69.2)	
T2	3 (5.0)	13 (7.4)	7 (6.5)	
T3	5 (8.3)	24 (13.6)	22 (20.6)	
T4	3 (5.0)	2 (1.1)	4 (3.7)	
N-stage				0.644
N0	59 (98.3)	169 (96.0)	102 (95.3)	
N1	1 (1.7)	7 (4.0)	5 (4.7)	
M-stage				0.102
M0	58 (96.7)	171 (97.2)	98 (91.6)	
M1	2 (3.3)	5 (2.8)	9 (8.4)	
Fuhrman grade				**0.160**
I	10 (16.7)	34 (19.3)	11 (10.3)	
II	39 (65.0)	111 (63.1)	66 (61.7)	
III	11 (18.3)	28 (15.9)	25 (23.4)	
IV	0 (0.0)	3 (1.7)	5 (4.7)	
Hemoglobin (g/L), mean (SD)	140.90 (17.16)	135.28 (16.79)	125.26 (24.51)	<0.001
ALB, [g/L, mean (SD)]	44.93 (2.29)	40.88 (4.89)	39.27 (5.17)	<0.001
GLB, [U/L, mean (SD)]	24.39 (2.77)	29.43 (5.61)	30.30 (5.95)	<0.001
AGR [mean, (SD)]	1.87 (0.25)	1.43 (0.29)	1.35 (0.31)	<0.001
Survival time (months)	35.17 (18.80)	33.10 (19.58)	30.44 (17.73)	0.106

Continuous data are presented as the mean ± standard deviation and categorical data as n (%).

For categorical variables, P-values were analyzed by chi-square tests. For continuous variables, the t-test for slope was used in generalized linear models. For AJCC stage, T-stage, N-stage, M-stage, and Fuhrman grade, Fisher's exact test was used.

SD, standard deviation; BMI, Body mass index; AJCC, American Joint Committee on Cancer; ALB, albumin; GLB, globulin; AGR, albumin to globulin ratio; CAS, combination of albumin-globulin score and skeletal muscle index.

prognosis of RCC patients undergoing nephrectomy. This study revealed that a high CAS grade was associated with a poor prognosis. CAS was an independent prognostic risk factor for OS and CSS in RCC patients, and CAS had higher accuracy in predicting OS and CSS than AGR, AGS, and sarcopenia.

ALB and GLB are two important components of human serum proteins. Serum albumin is frequently used to determine the nutritional status of patients (15). Hypoalbuminemia in cancer patients is not only an indicator of malnutrition but is also associated with a systemic inflammatory response, which may be caused by cytokine-induced immunosuppression (16). Recent research has demonstrated that serum ALB levels can predict the prognosis of cancer patients. In addition, combination factors consisting of ALB and other indicators (such as C-reactive protein) can predict the prognosis of RCC patients (17, 18).

GLB is the major component of non-albumin proteins in serum, and the serum GLB component contains various proteins that are critical in immune and inflammatory responses, including immunoglobulins, complement, and some acute-phase response proteins (C-reactive protein, cytokines, etc.) (19). Increased GLB levels can be considered a marker of chronic inflammatory response, reflecting the accumulation of various pro-inflammatory cytokines (20).

Since ALB levels are associated with many factors, such as stress, liver insufficiency, and changes in body fluid volume, their clinical utility for predicting cancer patient prognosis is limited (21). In contrast, AGR is unaffected by the aforementioned factors. AGR is a new tumor predictor for upper tract urothelial carcinoma, esophageal squamous cell carcinoma, non-small

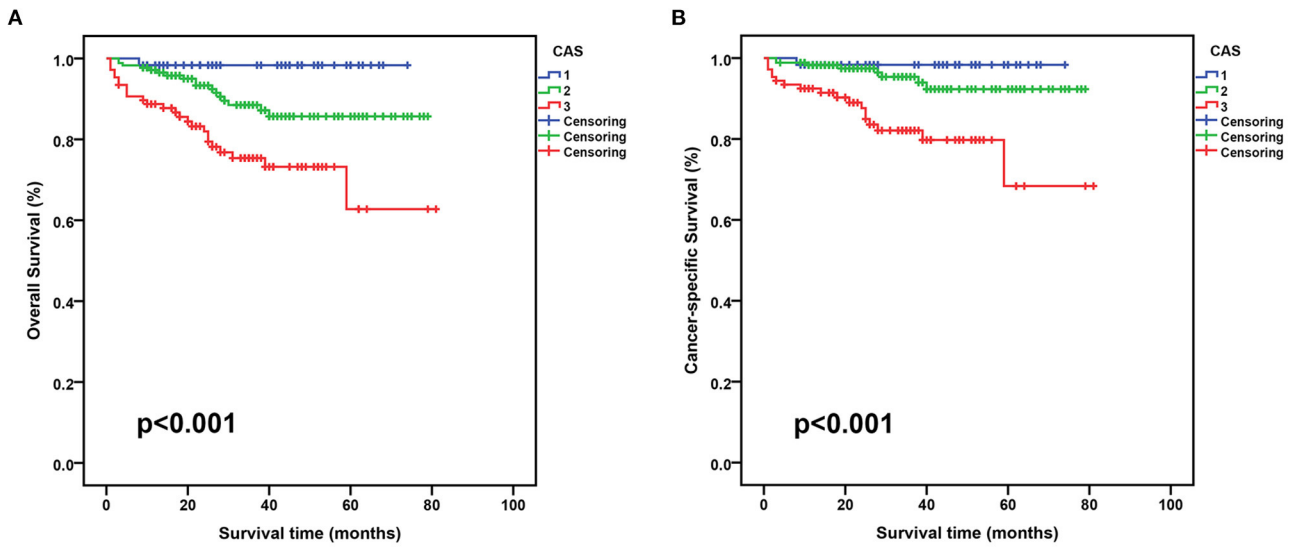

FIGURE 3 | Kaplan-Meier curves for OS and CSS stratified by CAS grade in the training set. **(A)**, CAS OS; **(B)**, CAS CSS. OS, overall survival; CSS, cancer-specific survival; CAS, combination of albumin-globulin score and sarcopenia.

TABLE 4 | Hazard ratios of overall survival (OS) and cancer-specific survival (CSS) was calculated according to CAS in training set[a].

Characteristic	Basic Model		Core Model		Extended Model	
	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Overall Survival						
CAS		<0.001		<0.001		<0.001
Grade 1	0.07 (0.01–0.48)	0.007	0.09 (0.01–0.67)	0.018	0.08 (0.01–0.58)	0.012
Grade 2	0.40 (0.21–0.73)	0.003	0.43 (0.23–0.80)	0.008	0.47 (0.25–0.88)	0.018
Grade 3	Reference		Reference		Reference	
Cancer-specific Survival						
CAS		<0.001		0.001		0.003
Grade 1	0.09 (0.01–0.67)	0.019	0.14 (0.02–0.93)	0.042	0.12 (0.02–0.94)	0.043
Grade 2	0.26 (0.11–0.59)	0.001	0.28 (0.12–0.66)	0.003	0.31 (0.13–0.71)	0.006
Grade 3	Reference		Reference		Reference	

[a]*Adjusted covariates: Basic model: age, gender, BMI, hypertension, diabetes, cardiovascular diseases and smoking; Core model: basic model plus surgery type and laterality; Extended model: core model plus AJCC stage, T stage, N stage, M stage and Fuhrman grade.*

BMI, Body mass index; AJCC, American Joint Committee on Cancer; aHR, adjusted hazard ratio; CI, confidence interval; CAS, combination of albumin-globulin score and skeletal muscle index.

cell lung cancer and other tumors (22–25). Meanwhile, the albumin-globulin score (AGS) has been proposed as another prognostic model to predict the prognosis of certain tumors, such as non-small cell lung cancer and esophageal squamous carcinoma (8, 26).

Sarcopenia is not a simple loss of weight or slimming tissue, but a progressive and widespread loss of skeletal muscle mass, strength, and body skeletal muscle. As the decline of skeletal muscle mass may be reversible, sarcopenia has important implications for guiding clinical practice (27). Some studies have demonstrated that establishing a regular exercise and nutritional support program before operation can lead to increased daily calorie and protein intake, as well as a significant increase in grip strength (28, 29). In the study, we found that 44.5% of the sarcopenia patients had BMI $\geq$ 25 kg/m^2. The coexistence of obesity and sarcopenia is increasing, and these people are also at risk of their complications (30). Additionally, sarcopenia is more prevalent in elderly patients, contributing to sarcopenia patients' increased risk of death. For lean patients with low BMI, early intervention and increased dietary supplements with protein, vitamin D and antioxidants can slow sarcopenia progression (31, 32).

To our knowledge, this is the first multicenter clinical study to explore the prognostic value of CAS in RCC patients undergoing nephrectomy. For calculating CAS grade, ALB, GLB, and SMI for calculating sarcopenia are more readily available clinically and less costly. In addition, CAS grade combines three indicators, ALB, GLB, and sarcopenia, to accurately reflect

TABLE 5 | Accuracy of AGR, AGS, SMI and CAS in predicting overall survival (OS) and cancer-specific survival (CSS) by assessing the area under the curve (AUC) in the training and test sets.

Characteristics		Training Set			Test Set		
		AUC	95% CI	*P*-value	AUC	95% CI	*P*-value
Overall survival	AGR	0.647	0.557–0.737	0.002	0.504	0.330–0.678	0.966
	AGS	0.583	0.500–0.667	0.077	0.527	0.354–0.699	0.766
	SMI	0.646	0.556–0.735	0.002	0.714	0.550–0.878	0.017
	NLR	0.611	0.520–0.702	0.019	0.477	0.305–0.649	0.799
	PLR	0.584	0.490–0.679	0.074	0.566	0.406–0.727	0.458
	CAS	0.687	0.607–0.766	<0.001	0.724	0.557–0.891	0.012
Cancer-specific survival	AGR	0.613	0.500–0.726	0.051	0.481	0.266–0.696	0.859
	AGS	0.590	0.490–0.689	0.122	0.571	0.372–0.769	0.509
	SMI	0.599	0.486–0.712	0.088	0.750	0.568–0.932	0.019
	NLR	0.631	0.522–0.741	0.024	0.478	0.272–0.684	0.703
	PLR	0.581	0.465–0.698	0.160	0.541	0.342–0.740	0.839
	CAS	0.710	0.613–0.808	<0.001	0.805	0.648–0.962	0.004

OS, overall survival; CSS, cancer-specific survival; CI, confidence interval; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index; CAS, combination of albumin-globulin score and skeletal muscle index.

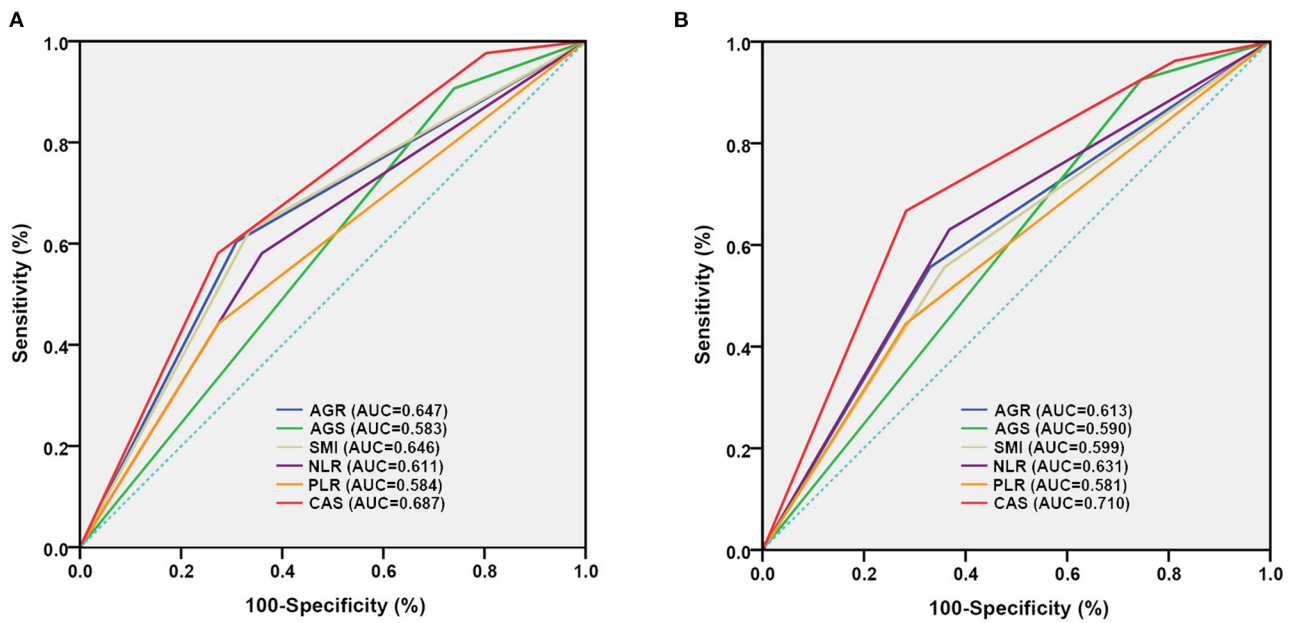

FIGURE 4 | Comparison of area under ROC curves for AGR, AGS, SMI and CAS grade in predicting OS and CSS in the training set. **(A)**, OS ROC curves; **(B)**, CSS ROC curves. OS, overall survival; CSS, cancer-specific survival; ROC, receiver operator characteristic; AUC, area under the curve; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index; CAS, combination of albumin-globulin score and sarcopenia.

patients' nutritional and inflammatory status and expand the predictive ability of individual indicators of ALB, GLB, or sarcopenia for RCC patients.

This study also has several limitations. First, we excluded other treatment modalities, which will have an impact on prognosis. Second, we did not assess the patient's quality of life, energy level, and postoperative nutritional status. Finally, although this is a multicenter study, it remained a retrospective study which requires a larger sample size than a prospective study.

CONCLUSION

We successfully constructed an index (CAS) that can more accurately predict the prognosis of RCC patients undergoing laparoscopic nephrectomy.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here. The datasets used and analyzed during the

current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The methodology of this study was ethically approved by the Ethics Committees and Institutional Review Boards of all participating institutions (SHSY-IEC-BG/02.04/04.0-81602469 and ZDKYSB077). 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

WM, JW, HZ, and MC conception and design. BX and MC administrative support. SS, ZX, JY, CW, SC, and BX collection and assembly of data. WM and KW data analysis and interpretation. WM, NZ, KW, and QH manuscript writing. All authors are final approval of manuscript.

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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.2021.731466/full#supplementary-material

Supplementary Figure 1 | Kaplan-Meier curves for OS and CSS stratified by AGR, AGS and SMI in the test set. **A** and **D**, AGR OS and CSS; **B** and **E**, AGS OS and CSS; **C** and **F**, SMI OS and CSS. OS, overall survival; CSS, cancer-specific survival; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index.

Supplementary Figure 2 | Kaplan-Meier curves for OS and CSS stratified by CAS grade in the test set. **A**, CAS OS; **B**, CAS CSS. OS, overall survival; CSS, cancer-specific survival; CAS, combination of albumin-globulin score and sarcopenia.

Supplementary Figure 3 | Comparison of area under ROC curves for AGR, AGS, SMI and CAS grade in predicting OS and CSS in the test set. **A**, OS ROC curves; **B**, CSS ROC curves. OS, overall survival; CSS, cancer-specific survival; ROC, receiver operator characteristic; AUC, area under the curve; AGR, albumin to globulin ratio; AGS, albumin-globulin score; SMI, skeletal muscle index; CAS, combination of albumin-globulin score and sarcopenia.

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Association Between Phase Angle and Sarcopenia in Patients Undergoing Peritoneal Dialysis

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Introduction: There is limited data on the association between phase angle (PhA) and sarcopenia using both muscle strength and muscle mass in patients undergoing peritoneal dialysis (PD). We aimed to evaluate the association between PhA and sarcopenia in patients undergoing PD.

Methods: We enrolled prevalent patients undergoing PD ($n = 200$). The patients were divided into tertiles based on their PhA level: low ($n = 66$; 1.9–4°), middle ($n = 68$; 4.1–4.9°), and high tertiles ($n = 66$; 5–8°). PhA was measured by a bioimpedance analysis. Handgrip strength (HGS) was measured in all the patients. Body compositions were measured by dual energy x-ray absorptiometry (DXA).

Results: Handgrip strength (HGS) and/or lean mass indices showed poorer trends in the low tertile than in the other tertiles. PhA was positively associated with HGS and/or muscle mass index. Multivariate analyses showed that the patients in the low tertile had an odds ratio of 9.8 ($p = 0.001$) and 52.79 ($p < 0.001$) for developing sarcopenia compared with those in the middle and high tertiles, respectively. Subgroup analyses using these variables yielded results similar to those from the total cohort.

Conclusion: This study demonstrated that PhA is independently associated with muscle mass, strength, and sarcopenia in patients undergoing PD. This result suggests that PhA can be used as a valuable and simple predictor for identifying patients undergoing PD who are at risk of sarcopenia.

Keywords: peritoneal dialysis, sarcopenia, muscle mass, handgrip strength, bioimpedance

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INTRODUCTION

Sarcopenia is one of the most important complications in patients undergoing peritoneal dialysis (PD), with a prevalence of 8–15.5% (1–3). Sarcopenia is a progressive and generalized muscle disorder associated with increased falls, fractures, physical disability, and mortality (4), and it is classically defined as a combination of low muscle mass and low strength (4–6). Muscle strength is not affected by muscle mass alone, and the association between muscle mass and strength is not linear (6). This leads to the application of two indicators to diagnose sarcopenia in clinical practice. Sarcopenia was originally considered as results of the aging process.

However, recent studies have shown that inflammatory processes, such as malignancy and organ failure, can give rise to sarcopenia (4). Sarcopenia in patients undergoing PD is caused by various factors such as anorexia, uremic toxin, volume overload, or peritoneal dialysate (7), and it is strongly associated with the risk of falls, fractures, disability, and decreased cognition (8, 9). Two previous studies on patients undergoing dialysis have reported a hazard ratio of 1.93 and 2.92, respectively, for mortality in patients with sarcopenia than those without sarcopenia (10, 11). Pereira et al. included 287 patients with non-dialysis chronic kidney disease, among whom 17 had sarcopenia, and reported a hazard ratio of 3.02 in patients with sarcopenia compared with those without sarcopenia (12). Interventions, such as nutritional supplementation or exercise, can be applied to patients who are at high risk of sarcopenia. Some studies have shown favorable effects on protein homeostasis, exercise tolerance, quality of life, dialysis adequacy, and physical performance through nutritional support or exercise (13, 14). These findings reveal that the early diagnosis of sarcopenia can be useful in improving the prognosis of patients undergoing dialysis who have a high risk of sarcopenia. However, diagnostic methods may be difficult to apply to all patients. Recent guidelines have shown the usefulness of questionnaires, such as SARC-F, as a screening method. Still, the method has a very low positive predictive value in patients undergoing PD (4, 15). This limitation may require additional indicators to predict sarcopenia, especially the direct or indirect evaluation of muscle mass.

The bioimpedance analysis (BIA) is a popular body composition analysis technique and is well-validated for use in the general population. It is a non-invasive method for assessing the resistance and reactance in various regions and frequencies (generally between 1 and 1,000 kHz). The impedance measured using this device shows the bioelectrical characteristics of patients. Bioimpedance at currents of various frequencies is used to calculate body composition, estimated from regression equations derived from a healthy population (16). Recent guidelines recommend estimating muscle mass using a bioimpedance analysis (BIA) to diagnose sarcopenia (4). However, the body composition calculated from a BIA might not be accurate in populations with various diseases, especially volume-dependent patients such as those undergoing dialysis. A previous study showed a significant bias between muscle mass measurements using a BIA and the standard method in volume-dependent patients (17). The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-DOQI) guidelines reported a lack of evidence to recommend measuring body composition using a BIA. The guidelines also stated that body composition measurement data obtained using a BIA should be interpreted cautiously in a patient undergoing PD (18). Therefore, phase angle (PhA) as raw data with no regression equation can be an alternative method to predict various conditions. The PhA is regarded as a biological marker of cellular health, and the association between PhA and malnutrition or mortality in non-dialysis patients is well-known. Some studies showed the association between PhA and mortality or malnutrition in patients undergoing PD. These studies demonstrated a positive association between PhA and nutritional indices, such as subjective global assessment measurement, serum albumin, total protein, creatinine, blood urea nitrogen, prealbumin, and a Geriatric Nutritional Risk Index (GNRI) in patients undergoing PD (19–22). Furthermore, the associations with residual renal function, lean mass index, or mortality were obtained from previous studies (22, 23). However, most malnutrition indices in these studies were defined by body composition measurements from a BIA or an incomplete definition for sarcopenia (19–23). There were few data on the association between PhA and sarcopenia using both muscle strength and muscle mass. Although volume overloading can lead to the overestimation of fat-free mass by dual energy x-ray absorptiometry (DXA), the NKF-DOQI guidelines recommend that body composition measurement by DXA is reasonable in patients undergoing PD as it remains the gold standard for measuring body composition (18, 24). In addition, a BIA can be considered an alternative method to predict muscle mass in the guidelines for diagnosing sarcopenia. Although both DXA and BIA can be influenced by volume status, DXA has been validated and performed for direct measurements compared with a BIA. The European Working Group on Sarcopenia in Older People guidelines recommends DXA as a preferred method to diagnose sarcopenia (6). Muscle mass measurements using a more accurate method such as DXA, rather than BIA and muscle strength would be essential to evaluate the association between PhA and sarcopenia in patients undergoing PD. Thus, we aimed to evaluate the association between PhA and sarcopenia in patients undergoing PD.

METHODS

Study Population

This study was retrospective and cross-sectional, and it used data from a tertiary medical center. In our center, handgrip strength (HGS), body composition measurement using DXA, and BIA measurements for volume status were routinely evaluated for all PD patients, followed by the outpatient department from September 2017. All the patients undergoing PD were informed of the necessity of evaluating sarcopenia, and the evaluation was performed if a patient agreed to the measurement. Three measurements were simultaneously performed on the same day of the peritoneal equilibration test at 6–12 month intervals. A trained nurse performed all the measurements during the study period. We evaluated these indicators, which have been used for patient management and advice. We planned analyses using data from the patients undergoing PD who also underwent all HGS, BIA, and DXA measurements on the same day from September 2017 to November 2020. Therefore, the size of the sample was not determined. There were 214 prevalent patients undergoing PD between September 2017 and November 2020, among whom 14 were excluded because of missing data ($n = 8$), the inability to ambulate, or having an amputated limb ($n = 6$). Therefore, 200 patients undergoing PD were included in this study. We used the most recent data from the three measurements on the same day if a patient had multiple measurements at two or more different time points. Finally, the patients were divided into tertiles based

on the level of PhA as follows: low, middle, and high tertiles. The study was approved by the Institutional Review Board of Yeungnam University Medical Center (approval no: 2020-06-002). The board waived the need to obtain informed consent because the records and information of the participants were anonymized and de-identified prior to the analysis. The study was conducted ethically in accordance with the Declaration of Helsinki of the World Medical Association.

Baseline Variables

Baseline data on age, sex, presence of diabetes mellitus (DM), dialysis modality, dialysis vintage (months), body mass index (kg/m^2), weekly Kt/V_{urea}, C-reactive protein (mg/dl), 4-h dialysate-to-plasma creatinine concentration ratio, urine volume (ml/day), edema index, serum calcium (mg/dl), phosphorus (mg/dl), sodium (mEq/L), potassium (mEq/L), and albumin (g/dl) levels were collected. DM was defined as a patient-reported history and a medical record of a DM diagnosis or medication. Weekly Kt/V_{urea} was calculated using 24-h urine and dialysate as previously published (25). Four-hour dialysate-to-plasma creatinine concentration ratio (DP4Cr) was evaluated using a modified 4.25% peritoneal equilibration test, and the level was calculated using the creatinine level of the drained dialysate 4 h after injection per the blood creatinine level. The edema index was defined as extracellular water/total body water from BIA measurements.

Assessment of Nutritional Markers

PhA was measured using a multi-frequency BIA (InBody 770; InBody, Seoul, Korea). The value was calculated using an angle value of the time delay between the voltage waveform at 50 kHz and the current waveform. Briefly, the peritoneal dialysate was drained from the abdomen prior to measurement. Each subject was clothed with a light gown, and the bladder was emptied. Measurements were performed after rest for 5 min in the erect position. Eight electrodes were placed, two for each foot and two for each hand, with the patient in the erect position. Using reactance (Xc) and resistance (R) obtained from the BIA at 50 kHz, PhA was estimated by the following formula: PhA (°) = arctangent (Xc/R) × (180/p).

HGS was measured in all the patients. Each patient performed three trials with the dominant hand using a digital dynamometer (Takei 5401; Takei Scientific Instruments Co., Ltd., Niigata, Japan). The maximum strength measured over the three trials was recorded. Body compositions were measured using a DXA system (Hologic, Madison, WI, United States). The total lean mass (LM), appendicular lean mass (ALM), and total fat mass (FM) were estimated using this DXA system. The ALM was calculated using the sum of the lean masses of both extremities. The index values were defined as the value per height square. The visceral fat area (VFA, cm^2) was measured from the BIA, and a previous study showed a strong correlation between measurements from the BIA and those from standard methods (26). The normalized protein nitrogen appearance (nPNA, g/kg/day) and the Geriatric Nutritional Risk Index (GNRI) were calculated from previously described equations (27, 28).

Sarcopenia was defined using cut-off values from the Asian Working Group for Sarcopenia (5). Patients with low muscle mass (ALM index <7 kg/m^2 for men and <5.4 kg/m^2 for women by DXA) and low HGS (<26 kg for men and <18 kg for women) were classified as having sarcopenia.

Statistical Analysis

The data were analyzed using the statistical software IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, United States). Categorical variables were expressed as counts (percentages). Continuous variables were expressed as mean ± SD or SE. For continuous variables, means were compared by one-way ANOVA, followed by a Bonferroni *post-hoc* comparison and an analysis of covariance for multivariate analyses. The correlation between two continuous variables was assessed by Pearson's or partial correlation analysis. Linear or logistic regression analyses were performed to assess the independent predictors of nutritional indices or sarcopenia. A multivariate analysis was adjusted for age, sex, the presence of DM, BMI, urine volume, and edema index. The area under the receiver operating characteristic curve (AUROC) was used to calculate the probability to predict sarcopenia, cutoff values, sensitivity, and specificity. The best cutoff value was calculated using the Youden index in the AUROC. The MedCalc version 11.6.1.0 software (MedCalc, Mariakerke, Belgium) was used for the AUROC. The level of statistical significance was set at $p < 0.05$.

RESULTS

Clinical Characteristics of the Participants

The PhA intervals in the low, middle, and high tertiles were 1.9–4, 4.1–4.9, and 5–8°, respectively. The patients in the high tertile were younger than those in the other tertiles, and the proportion of female sex or DM was lowest in the high tertile. BMI, urine volume, and serum albumin levels were higher in the high tertile than in the other tertiles (**Table 1**). Among the patients, those in the high tertile had the lowest edema index. There were no significant differences in the use of automated PD, dialysis vintage, and weekly Kt/V_{urea} and the levels of C-reactive protein, DP4Cr, calcium, phosphorus, sodium, and potassium among the three tertiles.

Comparison of Nutritional Indices According to PhAs

In the univariate analyses, the values of HGS in the low, middle, and high tertiles were found to be 18.7 ± 6, 22 ± 6.8, and 30.5 ± 9 kg, respectively ($p < 0.001$). In the multivariate analyses, HGS values in the low, middle, and high tertiles were found to be 21.4 ± 0.9, 23 ± 0.7, and 26.5 ± 1 kg, respectively ($p = 0.006$, **Figure 1**). In the multivariate analyses, total LM index, and VFA were 15 ± 0.2 kg/m^2 and 92.8 ± 3.4 cm^2 in the low tertile, 15.4 ± 0.1 kg/m^2 and 82.9 ± 2.6 cm^2 in the middle tertile, and 15.9 ± 0.2 kg/m^2 and 57.2 ± 3.7 cm^2 in the high tertile, respectively (**Table 2**) (p =0.027 for total LM index and $p < 0.001$ for VFA). HGS was greatest in the patients in the high tertile. The total

TABLE 1 | Clinical characteristics of the participants.

	Total ($n = 200$)	Low tertile ($n = 66$)	Middle tertile ($n = 68$)	High tertile ($n = 66$)	*p*
Age (years)	55.5 ± 12.2	59.4 ± 11.7	57.3 ± 11.2	49.7 ± 11.9*#	<0.001
Sex (men)	114 (57.0%)	30 (45.5%)	35 (51.5%)	49 (74.2%)	0.002
Diabetes mellitus (%)	99 (49.5%)	41 (62.1%)	37 (54.4%)	21 (31.8%)	0.001
Automated peritoneal dialysis	58 (29.0%)	14 (21.2%)	21 (30.9%)	23 (34.8%)	0.206
Dialysis vintage (months)	57.8 ± 53.2	63.1 ± 52.3	55.4 ± 52.2	55.1 ± 55.3	0.624
Body mass index (kg/m^2)	24.7 ± 3.8	24.1 ± 3.1	24.1 ± 3.8	25.8 ± 4.1*#	0.011
Weekly Kt/Vurea	1.92 ± 0.46	1.93 ± 0.43	1.86 ± 0.43	1.98 ± 0.52	0.382
C-reactive protein (mg/dL)	0.57 ± 1.26	0.62 ± 1.42	0.66 ± 1.47	0.42 ± 0.75	0.491
DP4Cr	0.66 ± 0.13	0.69 ± 0.16	0.64 ± 0.11	0.65 ± 0.12	0.090
Urine volume (ml/day)	430 ± 603	361 ± 574	236 ± 385	697 ± 717*#	<0.001
Edema index	0.400 ± 0.013	0.412 ± 0.009	0.400 ± 0.007*	0.387 ± 0.009*#	<0.001
Serum calcium (mg/dL)	8.3 ± 0.9	8.3 ± 0.9	8.3 ± 1.0	8.3 ± 1.0	0.980
Serum phosphorus (mg/dL)	4.9 ± 1.4	4.7 ± 1.4	5.0 ± 1.3	5.0 ± 1.4	0.599
Serum sodium (mEq/L)	136 ± 4	136 ± 4	136 ± 4	137 ± 3	0.342
Serum potassium (mEq/L)	4.5 ± 0.7	4.5 ± 0.8	4.6 ± 0.6	4.6 ± 0.6	0.428
Serum albumin (g/dL)	3.6 ± 0.5	3.3 ± 0.5	3.6 ± 0.4*	3.8 ± 0.4*#	<0.001

Data are expressed as mean ± SD for continuous variables and as numbers (percentages) for categorical variables. P-values were tested using a one-way ANOVA, followed by Bonferroni's post-hoc comparison for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables.
DP4Cr, 4-h dialysate-to-plasma creatinine concentration ratio.
$^*p < 0.05$, compared with low tertile and $^{\#}p < 0.05$, compared with middle tertile.

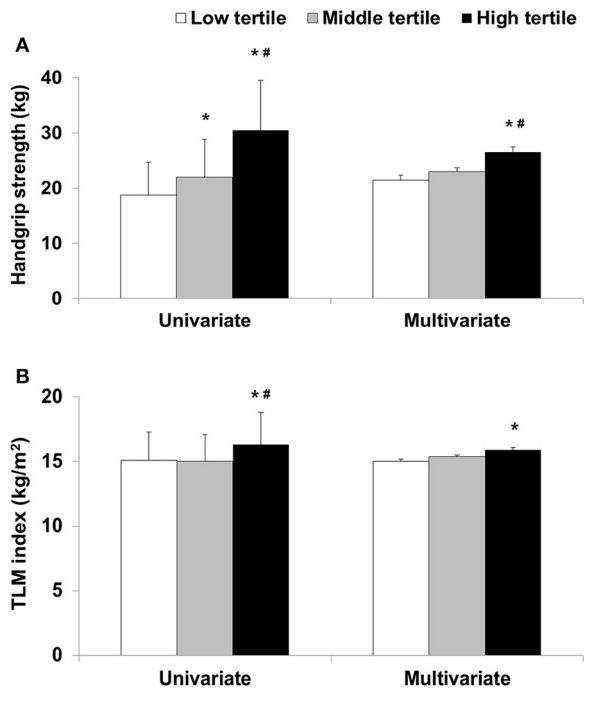

FIGURE 1 | (A) Handgrip strength or **(B)** total lean mass (TLM) index according to phase angle tertile. $^*p < 0.05$ compared with low tertile and $^{\#}p < 0.05$ compared with middle tertile.

LM index was lower in the patients in the low tertile than those in the high tertile. VFA was lowest in the patients in the high tertile. Among the patients, those in the low tertile had the lowest nPNA. The ALM index and GNRI were lowest in the patients in the low tertile, but the difference was not statistically significant. PhA, as a continuous variable, was positively associated with HGS, total LM index, ALM index, total FM index, nPNA, and GNRI (**Supplementary Table 1**). The partial correlation adjusted for covariates showed positive associations with HGS, total LM index, ALM index, and nPNA, and showed inverse associations with total FM index and VFA. Linear regression analyses also showed positive associations between PhAs and both HGS and the ALM index as two indicators of sarcopenia in univariate and multivariate analyses (**Supplementary Table 2**).

Comparison of Nutritional Indices According to PhAs

Prevalence of Sarcopenia

The number of patients with low muscle mass in the low, middle, and high tertiles was 42 (63.6%), 47 (69.1%), and 33 (50%), respectively ($p = 0.067$). The number of patients with low HGS in the low, middle, and high tertiles was 55 (83.3%), 32 (47.1%), and 8 (12.1%), respectively ($p < 0.001$). The number of patients with sarcopenia in the low, middle, and high tertiles was 35 (53%), 23 (33.8%), and 6 (9.1%), respectively ($p < 0.001$) (**Figure 2**). Among the three tertiles, the proportion of patients with low HGS or sarcopenia was highest in the low tertile. A multivariate logistic regression analysis showed that the patients in the low tertile had an odds ratio of 9.8 ($p = 0.001$) and 52.79 ($p < 0.001$) for developing sarcopenia compared with those in the middle and high tertiles, respectively (**Table 3**). The patients in the middle tertile had a 7.52 ($p = 0.011$) odds of developing sarcopenia compared with those in the high tertile.

TABLE 2 | Comparison of muscle mass indices and nutritional and physical activity markers according to the tertiles of phase angle.

	Univariate				Multivariate			
	Low tertile	**Middle tertile**	**High tertile**	***p***	**Low tertile**	**Middle tertile**	**High tertile**	***p***
ALM index (kg/m^2)	5.9 ± 1.1	6.0 ± 1.1	7.0 ± 2.9$^{*\#}$	<0.001	6.0 ± 0.3	6.2 ± 0.2	6.7 ± 0.3	0.357
TFM index (kg/m^2)	6.9 ± 2.2	7.3 ± 2.6	7.6 ± 2.5	0.286	7.6 ± 0.2	7.4 ± 0.2	6.8 ± 0.2	0.065
VFA (cm^2)	78.9 ± 30.4	80.9 ± 35.9	72.8 ± 36.4	0.371	92.8 ± 3.4	82.9 ± 2.6	57.2 ± 3.7$^{*\#}$	<0.001
nPNA (g/kg/day)	0.78 ± 0.21	0.85 ± 0.23	0.88 ± 0.17*	0.023	0.75 ± 0.03	0.85 ± 0.026*	0.92 ± 0.03*	0.006
GNRI	89.7 ± 9.7	94.2 ± 6.6*	97.1 ± 9.2*	<0.001	92.1 ± 1.4	94.9 ± 1.1	94.1 ± 1.5	0.223

Data are expressed as the mean ± SD for univariate analysis or the mean ± SE for multivariate analysis. P-values were tested by a one-way ANOVA, followed by a Bonferroni post-hoc comparison on the univariate analyses and an analysis of covariance on the multivariate analyses. Multivariate analyses were adjusted for age, sex, the presence of diabetes mellitus, body mass index, urine volume, and edema index.

ALM, appendicular lean mass; TFM, total fat mass; VFA, visceral fat area; nPNA, normalized protein equivalent of total nitrogen appearance; GNRI, Geriatric Nutritional Risk Index.

$^{*}p < 0.05$ compared with low tertile and $^{\#}p < 0.05$ compared with middle tertile.

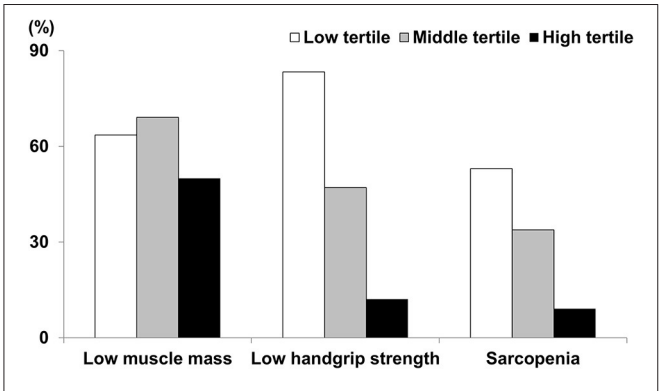

FIGURE 2 | Proportions of patients with low muscle mass, low handgrip strength, or sarcopenia.

AUROC of PhA for Sarcopenia

The AUROC of PhA for sarcopenia was 0.73 (95% CI,0.67–0.79, $p < 0.001$, **Figure 3**). The sensitivity and specificity in predicting sarcopenia were 81.3% (95% CI, 69.5–89.9) and 59.6% (95% CI, 50.8–67.9), respectively. The optimal cut-off value was identified as ≤4.4°.

Subgroup Analyses According to Age, Sex, and Presence of DM

We divided the patients into two age groups according to the median age of 55 years. For those aged <55 years, most of the variables except nPNA in the univariate analysis and GNRI in the multivariate analyses were significantly associated with PhA (**Supplementary Table 3**). In the multivariate analyses, all the variables except nPNA were statistically significant in those aged ≥55 years, with similar trends in those aged <55 years. In the analyses by sex or DM, all the variables except GNRI were associated with PhA in the multivariate analysis (**Supplementary Tables 4, 5**).

DISCUSSION

PhA is associated with the quantity of cell mass or cell membrane integrity (29). A high PhA reveals greater cellularity and relatively less water content to cell mass, which results in a low extracellular water/intracellular water ratio (30). Malnutrition caused by various diseases can lead to a shift from intracellular water to extracellular water and a decrease in cell mass. These changes result in a decrease in the level of PhA (30, 31). Therefore, previous studies have evaluated the association between PhA and malnutrition in various diseases or sarcopenia. This study also revealed that high PhA tertiles were associated with high HGS, total LM index, or nPNA. Patients with low PhA tertiles had greater sarcopenia, and PhA values, as continuous variables, were also correlated with HGS, total LM index, ALM index, and nPNA. Similar trends were obtained from linear regression analyses or subgroup analyses.

Previous studies have shown the association between PhA and nutritional status or sarcopenia under various conditions. Espirito Santo Silva et al. enrolled patients with liver cirrhosis and evaluated muscle mass by DXA and muscle strength using HGS (32). They showed an inverse association between PhA and sarcopenia and an angle ≤5.05° as a cutoff value for nutritional complication in patients with liver cirrhosis. Sarcopenia is originally defined as an age-related decline in muscle mass and is highly prevalent in the elderly population. Some studies on the elderly population showed a significant association between PhA and sarcopenia by muscle mass measurement (using ultrasonography or BIA) and HGS (33–35). Marini et al. evaluated an elderly population and showed a positive association between PhA and skeletal muscle mass index (36). However, muscle mass alone was evaluated by DXA. Two studies enrolled hospitalized patients and showed a positive association between PhA and sarcopenia combined with muscle mass using BIA, CT, and HGS (37, 38). Cancer is a well-known risk factor for sarcopenia. Pérez Camargo et al. evaluated palliative patients with cancer and revealed an association between PhA and muscle mass using a BIA (39). Souza et al. showed that PhA is a marker for muscle mass index, muscle density, and HGS in patients with colorectal cancer (40). Although kidney transplant recipients have favorable muscle mass or strength compared with patients undergoing dialysis, steroids or suboptimal renal function can lead to a negative balance of muscle mass (41). Two studies using kidney transplant recipients revealed a positive association between PhA and muscle strength or sarcopenia (42, 43).

TABLE 3 | Logistic regression analysis for sarcopenia according to variables.

	Univariate		Multivariate	
	Odds ratio (95% CI)	***p***	**Odds ratio (95% CI)**	***p***
Age (per 1 year increase)	1.05 (1.02–1.08)	<0.001	1.04 (1.01–1.07)	0.023
Sex (ref: men)	1.15 (0.63–2.09)	0.651	0.43 (0.19–0.99)	0.046
Diabetes mellitus	1.36 (0.75–2.47)	0.315	1.28 (0.57–2.86)	0.553
BMI (per 1 kg/m^2 increase)	0.80 (0.72–0.89)	<0.001	0.77 (0.67–0.89)	<0.001
Urine volume (per 1 ml/day increase)	1.00 (1.00–1.00)	0.335	1.00 (1.00–1.00)	0.795
Edema index (per 0.01 increase)	1.37 (1.08–1.74)	0.010	0.53 (0.32–0.87)	0.012
Tertile by phase angle				
Low tertile (ref: Middle tertile)	2.21 (1.10–4.44)	0.026	9.86 (2.49–39.02)	0.001
Low tertile (ref: High tertile)	11.29 (4.29–29.74)	<0.001	52.79 (8.84–315.19)	<0.001
Middle tertile (ref: High tertile)	5.11 (1.92–13.59)	0.001	7.52 (1.60–35.35)	0.011

Multivariate analysis was adjusted for age, sex, presence of diabetes mellitus, body mass index, urine volume, and edema index.
CI, confidence interval; BMI, body mass index.

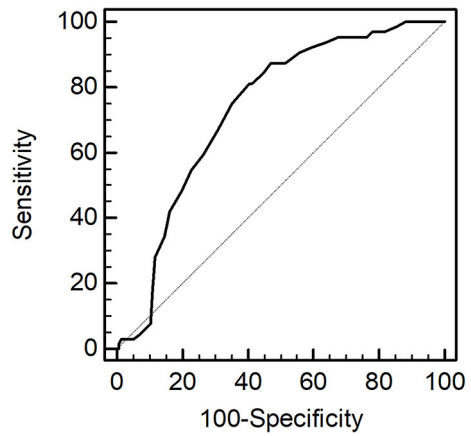

FIGURE 3 | Receiver operating characteristic curve of phase angle used to predict sarcopenia.

Some studies evaluated the association between PhA and nutritional markers such as serum albumin or muscle mass measurements using a BIA in patients undergoing PD. Passadakis et al. showed a positive association between PhA and subjective global assessment as nutritional index in 47 patients undergoing PD (19). Fein et al. showed a positive correlation between PhA and albumin, total protein, and creatinine in 45 patients undergoing PD (20). Mushnick et al. enrolled 48 patients undergoing PD and showed that PhA is associated with patient survival and serum albumin level (21). A study from Korea enrolled 80 patients undergoing PD and showed that PhA was correlated with serum albumin, GNRI, and LM index from bioimpedance (22). However, in this study, muscle mass was evaluated using bioimpedance, and there were no data on muscle strength. Huang et al. enrolled a large sample of 760 patients undergoing PD and showed that low PhA is associated with high mortality, serum albumin, creatinine, and favorable residual renal function in patients undergoing PD (23).

The results of this study were similar to those from previous studies. PhA was associated with sarcopenia and/or each component of sarcopenia. The inverse association was stronger in muscle strength than muscle mass. We considered the effect of the volume on the LM index, and multivariate analyses were adjusted for edema index. In this study, PhA showed a different association with lean mass or fat mass. Although it is not well-known whether a high fat mass in patients undergoing dialysis is favorable, a high fat mass can be useful to prevent malnutrition. However, fat mass *per se* would be a hazard to overall cellular health and may be expressed as low PhA in patients undergoing PD.

In this study, we found no association between PhA and GNRI in the multivariate analysis. This may be caused by the strong association between GNRI and serum albumin. In particular, GNRI is calculated using body weight and serum albumin, which can be largely influenced by serum albumin (28). Serum albumin is a commonly used nutrition index, but it has many limitations in predicting nutritional status. It is also considered a negative acute phase protein and is inversely associated with volume status and inflammation. In addition, serum albumin may be normal in mildly malnourished patients because of hepatic adaptation according to malnutrition (44).

This study has several strengths. Several previous studies on sarcopenia have used incomplete criteria for sarcopenia, such as muscle mass alone. The muscle mass from previous studies has been estimated by anthropometry or with BIA or equations using creatine kinetics (19–23). Recent guidelines for diagnosing sarcopenia recommend both BIA and DXA as reasonable for assessing muscle mass (4, 5). However, patients undergoing PD have more volume overload than patients undergoing hemodialysis (45). A guideline suggests that performing DXA would be more reasonable than using a BIA to measure muscle mass in patients undergoing PD. First, this study enrolled patients who were undergoing PD alone as a single dialysis modality and included a relatively large sample size. Second, we used consensus definitions

and cut-off values for Asian populations (5). Third, muscle mass measurements were evaluated by DXA, and sarcopenia was defined using two variables (low strength and low muscle mass). Considering the importance of the proper screening of sarcopenia in patients undergoing PD or the findings, PhA may be useful for deciding whether further evaluation is required to diagnose sarcopenia in patients undergoing PD.

This study has inherent limitations, namely, its single center and retrospective nature. It could not evaluate the causal relationship between variables and was not planned for a diagnostic study. A sample size calculation was not performed. However, owing to the relatively large sample size, the design of this study can be applied to evaluate the association between variables. Although this study showed an association between PhA and sarcopenia or sarcopenia-associated indicators in patients undergoing PD, it did not present the diagnostic efficacy of PhA for sarcopenia, such as sensitivity, specificity, and positive/negative predictive values. In addition, the use of PhA cannot easily diagnose sarcopenia because PhA value is not included in the diagnostic criteria for sarcopenia. Furthermore, the measurement of PhA requires a BIA machine, which is not available in all clinical settings. These findings reveal that the results of this study alone cannot provide sufficient evidence to predict or diagnose sarcopenia with PhA measurement. PhA could be considered an additional marker to suspect sarcopenia in patients at risk rather than a diagnostic property regarding these limitations. In addition, muscle mass measurement by DXA can be influenced by volume status. Baseline characteristics were significantly different among the three tertiles. Factors such as age, sex, and DM basically influence PhA, and patients with different PhAs will have different characteristics for these factors. However, we tried to attenuate these confounding factors by multivariate or subgroup analyses. A prospective longitudinal study that includes volume-independent muscle measurement and a larger number of patients is warranted to overcome these limitations.

This study demonstrated that PhA is independently associated with muscle mass, strength, and sarcopenia in patients undergoing PD. The results suggest that PhA can be used as a valuable and simple predictor for identifying patients undergoing PD who are at risk of sarcopenia.

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 IRB of Yeungnam University Medical Center (approval No: 2020-06-002). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SK conceptualized and designed the study, performed the data analysis and interpretation, and wrote the manuscript. AK and JD generated and collected the data. SK and JD drafted and revised the manuscript. All the authors approved the final version of the manuscript.

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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.2021.742081/full#supplementary-material

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MRI-Derived Subcutaneous and Visceral Adipose Tissue Reference Values for Children Aged 6 to Under 18 Years

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The assessment of body composition in pediatric population is essential for proper nutritional support during hospitalization. However, currently available methods have limitations. This study aims to propose a novel approach for nutrition status assessment and introduce magnetic resonance imaging (MRI)-derived subcutaneous and visceral fat normative reference values. A total of 262 healthy subjects aged from 6 to 18 years underwent MRI examinations and anthropometric measurements. MRI images at the second lumbar vertebrae were used by two radiologists to perform the semi-automatic tissue segmentation. Based on obtained adipose tissue surface areas and body mass index (BMI) scores sex-specific standard percentile curves (3rd, 10th, 25th, 50th, 75th, 90th, 97th) and z-scores were constructed using LMS method. Additionally, 85th and 95th centiles of subcutaneous and visceral adipose tissue were proposed as equivalents of overweight and obesity. Bland-Altman plots revealed an excellent intra-observer reproducibility and inter-observer agreement. In conclusion, our findings demonstrate highly reproducible method and suggest that MRI-derived reference values can be implemented in clinical practice.

Keywords: subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), magnetic resonance imaging, nutritional assessment, age and sex dependent reference values, percentile charts, children

INTRODUCTION

Childhood overweight and obesity have been recognized as strong risk factors for the development of cardiovascular disease, diabetes mellitus, depression, and cancer in adulthood (1, 2). Thus, determining body tissue composition, particularly visceral, and subcutaneous adipose tissue compartments can be useful for the assessment of patient risk stratification. A proper development during the growth period requires an appropriate nutritional status, mainly in children with coexisting chronic cardiovascular or oncological diseases (3, 4). In routine clinical practice, the assessment of obesity grade and body fat content is based on anthropometric measures and indexes such as skinfold thickness, body mass index (BMI), or waist to hip ratio (WtHR) in comparison

to the healthy population. Currently, body impedance analysis (BIA), which enables algorithm-based estimation of adipose and lean body mass has been increasingly used. While these methods are convenient and accessible in clinical routine practice, their accuracy in reflecting malnutrition and capability to differentiate visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) compartments are limited (5–7). Anthropometric measurements tend to underestimate the incidence of obesity and malnutrition, especially with the coexistence of disease both during the initial assessment and over the longer-term following the treatment (8, 9). BIA is safe and demonstrates higher sensitivity than anthropometric methods, but underestimates the amount of adipose tissue in lean children and overestimates in obese ones (5). Although there are imaging methods including dual-energy x-ray absorptiometry (DXA) and computed tomography (CT) which directly discern body compartments with high accuracy, their role in the pediatric population is limited due to the radiation burden (10–12). Another diagnostic tool frequently used in children is magnetic resonance imaging (MRI). Due to the different magnetic properties of water and fat-bound protons, this radiation-free technique allows to assess lean and adipose tissue compartments (13–17). However, a dedicated MRI whole-body protocol for the assessment of nutritional status is highly costly and time-demanding thus is limited in clinical use. In this context, it seems crucial to establish a simple and fast method of VAT and SAT quantification using MRI which can be obtained during the regular diagnostic protocol. A method that meets these requirements was already validated in adult population fat quantification from a single CT and MRI slice at the L2-L3 vertebral level (18–22). With this approach, all adipose tissue measurements can be obtained from routine diagnostic protocol with high correlation to MRI whole-body examination adipose tissue volumes.

Considering the limitation of currently available methods, this study aimed to establish the gender-dependent reference normative values of MRI-derived visceral and subcutaneous adipose tissue in a healthy pediatric population, which can serve as reference standards in the evaluation of body composition in children and adolescence with nutrition disorders.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Ethics Committee the approved number of our project is NKBBN/443/2018. Eligible participants were children and adolescence aged 0–18 who underwent MRI examination of the abdomen or pelvis in the years 2010–2020. The local database was searched by use of the dedicated search engine MedStream Designer (MSD) and 1,315 records were found. Exclusion criteria included incorrect search by MSD (281), examinations without T2-weighted sequences (48), T2-weighted sequences distorted by artifacts (47), a history of oncological or hematological disease, hydronephrosis, ascites, glycogen storage diseases (520), patients post nephrectomy, or other surgical procedure (59). The remaining 24 MRI records were follow up studies thus were excluded from the analysis (23). The MRI examinations of children aged 0–5 were also excluded due to insufficient sample size (74). The final analysis included a total of 262 children or adolescence aged 6–18 years (111 girls, and 151 boys) without changes or with changes of benign origin.

Demographic Characteristics

Demographic characteristics included patients' age, weight, and height at time of MRI examination. BMI was calculated for each subject by dividing weight in kilograms by square of the height in meters.

Imaging Method

Three different MRI systems were used: two 1.5T systems Magnetom Aera and Magnetom Sola (Siemens Healthineers, Erlangen, Germany) and one 3.0T system Philips Achieva 3.0 TX (Philips Medical Systems Nederlands, Best, Netherlands). MRI examinations of the abdomen and/or pelvis were performed by using the standard protocols. A standard TSE T2-weighted sequence in the transverse plane was taken for analysis. A single slice at the level of the second lumbar vertebra was selected for visceral and subcutaneous adipose tissue evaluation.

Adipose Tissue Quantification

The fat tissue compartment was segmented into SAT and VAT. The SAT was defined as subcutaneous fat externally of the abdominal and back muscles. The VAT was defined as adipose tissue inside of the abdominal cavity, excluding fat depots within abdominal and back muscles and fat tissue extending beyond the posterior outline of the vertebral body. Both arms visible on the analysis page were excluded from adipose tissue quantification.

Semi-automatic body composition analysis was performed with the use of parametric Magnetic Resonance Imaging v1.2.31-b (pMRI) software. The program is freeware available at the website www.parametricmri.com. The T2-weighted sequence was loaded into pMRI and processed with the volumetric region of interest analysis module which allows for segmentation and volumetric quantification of adipose tissues. A single slice at the level of the second lumbar vertebra was selected for the assessment of adipose tissue. For the analysis of SAT and VAT signal intensity, thresholds were manually set. After signal intensity-based segmentation, all data sets were visually revised (**Figure 1**). Misclassified tissues were corrected by two operators. One hundred seventy-two sets by KM (2nd year of specialization in radiology) and ninety sets by MP (radiologist with 15 years of experience in MRI). The average time needed for analysis and correction of a single data set was ∼between 5 and 15 min. The example of segmented cross-section is presented in **Figure 1**.

Statistical Analysis

Statistical Analysis of MRI Images

Agreement of segmentation results between observers and intra-observer reproducibility were assessed by using the Bland-Altman plots. The limits of agreement of the Bland-Altman plots were defined as the mean differences ±90% confidence intervals. Statistical analysis was performed in R version 4.1.0.

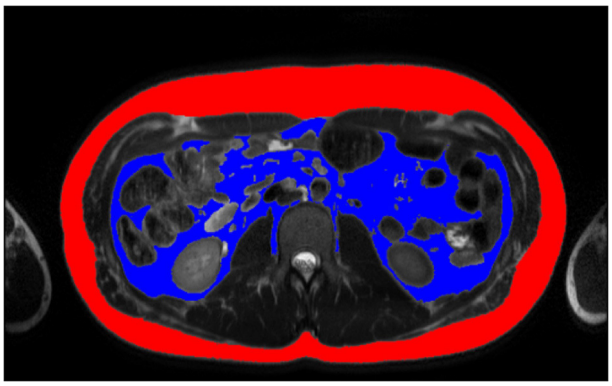

FIGURE 1 | Example of tissue SAT (red) and VAT (blue) segmentation of 14 years old boy, BMI: 27.7 kg/m^2 by MP. BMI, Body Mass Index, MP, second radiologist; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Statistical Analysis of Percentile Charts

Sex-specific BMI-for-age, SAT-for-age and VAT-for-age percentile curves and z-scores were constructed using the lambda-mu-sigma (LMS) method (24) and LMSChartMaker Light version 2.54 software (23). Identification of outliers was made by inspecting the z-score plot of each variable. None of the outliers were considered to be made due to mistakes of data recording or transferring. Following WHO guidelines (25, 26), derivation of percentiles was enabled only within the interval of z-scores between −3.0 and 3.0. To avoid assumptions about the distribution of data beyond the limits of observed values, the standard deviation at each age beyond this limit was fixed at the distance −2.5 SD and 2.5 SD correspondingly. In boys four SAT, three VAT, and one BMI values were fixed; in girls-only one SAT, two VAT, and one BMI values were fixed.

The LMS is based on the assumption that by use of Box-Cox transformation any anthropometric data such as BMI can be converted to a normal distribution for any given age (age was used as a continuous variable). Natural cubic splines with knots at each distinct age t were fitted to create three smooth curves representing the skewness L(t) [Box-Cox transformation], the median M(t), and the coefficient of variation S(t) of the original data as they vary with age:

$$C\alpha(t) = M(t)x[1 + L(t)xS(t)xZ\alpha]^{1/L(t)}$$

where Zα is the α-quantile of a standard normal distribution and Cα(t) is a percentile corresponding to Zα. Equivalent degrees of freedom (edf) L(t), M(t), and S(t) measure the complexity of each fitted curve. In our limited sample size, for each data set the standard edf of L3, M5, S3 was chosen, as further fitting made no significant improvements to our model (23).

RESULTS

The inter-observer agreement was assessed based on 15 sets of randomly selected MRI examinations segmented separately by both radiologists (KM and MP) (**Supplementary Figures 1, 2**). The same set of images was subsequently resegmented by one radiologist (K.M.) for the evaluation of the intra-observer reproducibility. Results in form of Bland-Altman plots are presented in the supplementary material (**Supplementary Figures 3, 4**). For SAT both intra- and inter-observer mean differences were at the level of 0.07 cm^2. The actual differences were up to 2 cm^2 for intra- and 0.5 cm^2 for inter-observer measurements which represents disagreement at a level of 1% for corresponding measurements. Slightly higher intra- and inter-observer disagreement was noted in VAT segmentation reaching accordingly up to 2.4 cm^2 (mean −0.04 cm^2) and 2.7 cm^2 (mean 0.08 cm^2). In those cases maximum difference in measurements was around 3%.

For the adjustment of BMI-for-age, SAT-for-age, and VAT-for-age percentiles the 262 MRI pediatric examinations (111 girls, and 151 boys) aged 6–18 (mean age of 12.49 years) were enrolled. The SAT and VAT reference values in each age group for boys and girls are presented in **Tables 1**–**4**. Based on the results percentile curves for SAT and VAT were calculated and presented in **Figures 2**–**5**.

Corresponding BMI growth charts are presented in the supplementary material in correlation to age (**Supplementary Figures 5, 6**). Among both genders, BMI increased continuously during childhood and adolescence, reaching a median of 22.5 kg/m^2 in boys and 21.7 kg/m^2 in girls at the end of the observed age range (18 years). In the groups between 8 and 10 years old, the flattening of the centile curves for BMI was observed, especially noticeable in the percentile range from 3 to 50.

The distribution of SAT percentiles were different between both genders. In boys, a continuous increase was observed throughout all age groups, reaching the median of 66.33 cm^2 at 18 years of age. In girls, at the beginning of maturity-onset (from age 7 to 11 years), a dynamic increase of SAT surface area was noted, which then stabilized at the age of 14 years (median of 91.1 cm^2).

For SAT, the difference between the 3rd and 97th percentile reached a maximum of 307.85 cm^2 for boys 12 years of age, while the maximum difference for girls (287.54 cm^2) was attained at 13 years of age (**Tables 1**, **2**).

The distribution of VAT percentiles was comparable for both genders. Both boys and girls showed a continuous increase in surface areas in all age groups, reaching the median of 55.08 cm^2 in boys and 48.41 cm^2 in girls at 18 years of age, respectively.

The difference of VAT areas between extreme percentiles increased continuously until age of 12 years in girls and until the end of the observed age range in boys. At this age, the difference of 81.15 and 137.14 cm^2, respectively, was attained, however in girls from 11 years onwards no substantial differences were noted (**Tables 3**, **4**).

DISCUSSION

This the first study which demonstrates the reference values of the subcutaneous and visceral adipose tissue as the percentile charts for girls and boys from 6 to 18 years of age.

TABLE 1 | SAT-for-age (cm^2) references for boys.

Age (years)	-2 SD	-1SD	1 SD	2 SD	P3	P5	P10	P25	P50	P75	P85	P90	P95	P97
6	12.59	16.65	32.90	50.62	13.00	13.86	15.34	18.37	22.84	29.03	33.38	36.86	43.04	47.88
7	11.93	17.64	47.90	94.22	12.47	13.63	15.71	20.29	27.80	39.65	48.96	57.03	72.69	86.13
8	12.37	20.17	71.96	174.74	13.07	14.60	17.45	24.06	35.83	56.40	74.04	90.25	123.97	155.09
9	13.82	23.94	100.41	274.09	14.69	16.64	20.33	29.19	45.72	76.26	103.69	129.70	185.76	239.42
10	15.10	27.26	123.36	342.98	16.13	18.45	22.89	33.69	54.22	92.71	127.52	160.58	231.70	299.44
11	15.53	28.92	135.35	368.56	16.66	19.20	24.08	36.05	58.90	101.63	139.91	175.90	252.16	323.41
12	15.35	29.27	139.05	367.50	16.52	19.15	24.23	36.72	60.54	104.67	143.67	179.89	255.33	324.37
13	15.12	29.39	140.52	360.87	16.31	19.00	24.21	37.04	61.42	106.13	145.11	180.88	254.24	320.19
14	15.04	29.69	142.40	357.15	16.26	19.02	24.37	37.55	62.53	107.89	146.98	182.51	254.45	318.21
15	15.04	30.07	144.48	355.74	16.29	19.12	24.61	38.13	63.70	109.76	149.07	184.53	255.64	317.96
16	15.06	30.43	146.40	355.33	16.34	19.23	24.84	38.67	64.76	111.45	151.01	186.47	257.04	318.37
17	15.08	30.72	147.97	355.13	16.38	19.32	25.03	39.12	65.63	112.84	152.59	188.07	258.23	318.79
18	15.09	30.95	149.23	354.93	16.40	19.38	25.18	39.47	66.33	113.95	153.86	189.33	259.14	319.09

P, percentile; SAT, subcutaneous adipose tissue; SD, standard deviation.

TABLE 2 | SAT-for-age (cm^2) references for girls.

Age (years)	-2 SD	-1SD	1 SD	2 SD	P3	P5	P10	P25	P50	P75	P85	P90	P95	P97
6	15.01	18.77	34.93	56.73	15.38	16.18	17.55	20.38	24.64	30.84	35.44	39.33	46.70	52.96
7	13.94	21.32	61.34	121.92	14.62	16.11	18.81	24.79	34.69	50.41	62.75	73.41	93.97	111.47
8	18.75	33.82	118.62	231.60	20.09	23.06	28.58	41.20	62.52	96.01	121.48	142.78	181.99	213.50
9	19.40	37.72	141.25	271.92	21.00	24.57	31.29	46.81	73.12	114.04	144.67	169.91	215.57	251.54
10	20.97	41.60	158.17	303.46	22.77	26.78	34.34	51.86	81.57	127.65	162.00	190.22	241.06	280.94
11	22.57	44.82	170.59	237.12	24.51	28.83	36.99	55.90	87.96	137.68	174.72	205.14	259.92	302.87
12	23.37	46.34	175.94	337.23	25.38	29.84	38.26	57.75	90.80	142.03	180.19	211.54	267.98	312.23
13	23.59	46.67	176.64	338.17	25.61	30.10	38.56	58.14	91.30	142.66	180.90	212.30	268.83	313.15
14	23.64	46.66	176.02	336.58	25.65	30.13	38.57	58.09	91.11	142.22	180.26	211.48	267.68	311.72
15	23.60	46.53	175.01	334.14	25.61	30.07	38.48	57.89	90.72	141.47	179.21	210.18	265.88	309.52
16	23.57	46.43	174.20	332.08	25.57	20.03	38.41	57.75	90.42	140.88	178.37	209.12	264.39	307.67
17	23.59	46.43	173.82	330.93	25.59	30.04	38.41	57.73	90.33	140.64	177.98	208.59	263.60	306.65
18	23.63	46.47	173.69	330.31	25.63	30.08	38.46	57.77	90.35	140.57	177.84	208.37	263.22	306.12

P, percentile; SAT, subcutaneous adipose tissue; SD, standard deviation.

Currently, the importance of adequate nutritional status during illness is strongly emphasized. Over the years a wide variety of VAT metabolic activity was confirmed highlighting the importance of the body composition assessment during treatment (27–29). Volume and distribution of adipose tissues determinate the type and intensity of malnutrition and therefore enable adequate nutritional support (30, 31).

Appropriate assessment of VAT in the pediatric population is considered to be a serious problem. Most of currently available measurement methods have limitations as discussed in the introduction (8, 9). In contrast, MRI enables direct, accurate, quantitative assessment of all compartments of body fat and is a radiation-free technique which allows safe and long-term observation in body composition changes during growth when compared to CT.

Our study plan was to use the safest method with high efficiency in the quantitative assessment of VAT and SAT. This can be done with MRI imaging which is a commonly used technique in pediatric population during the routine diagnostic process. The accuracy and reproducibility of the MRI examination in the assessment of adipose tissue have already been proved in both adult and pediatric patients (14, 32). The semi-automatic methodology used in our study is consistent with previous studies. In our study, SAT and VAT surface area results obtained by both radiologists on slices at the level of second lumbar vertebrae of randomly selected patients showed high intra-observer reproducibility and inter-observer agreement (**Supplementary Figures 1–4**). Both in SAT and VAT plots, the mean difference between radiologists was insignificant up to 2.5 cm^2 indicating that one of them selected larger areas as adipose

TABLE 3 | VAT-for-age (cm^2) references for boys.

Age (years)	-2 SD	-1SD	1 SD	2 SD	P3	P5	P10	P25	P50	P75	P85	P90	P95	P97
6	13.00	19.35	31.61	37.60	13.77	15.28	17.58	21.38	25.54	29.65	31.38	33.31	35.48	36.89
7	12.38	20.06	43.99	61.09	13.16	14.82	17.64	23.13	30.46	39.22	44.55	48.42	54.58	58.85
8	13.60	21.46	53.64	84.95	14.36	15.99	18.87	24.91	33.91	46.20	54.55	61.05	72.15	80.42
9	16.56	25.87	68.35	116.36	17.44	19.35	22.76	30.07	41.46	57.89	69.64	79.12	95.95	109.01
10	18.53	28.76	77.50	136.57	19.50	21.58	25.33	33.42	46.23	65.17	79.04	90.41	110.97	127.27
11	19.97	30.68	82.99	149.33	20.97	23.16	27.08	35.59	49.18	69.55	84.69	97.22	120.21	138.69
12	20.74	31.57	85.23	155.52	21.76	23.96	27.93	36.55	50.37	71.29	86.99	100.10	124.36	144.08
13	21.29	32.16	86.46	159.30	22.31	24.52	28.50	37.16	51.07	72.25	88.26	101.70	126.77	147.32
14	21.87	32.82	87.88	163.08	22.90	25.13	29.13	37.86	51.91	73.40	89.72	103.49	129.30	150.60
15	22.45	33.52	89.44	166.92	23.49	25.74	29.79	38.61	52.84	74.67	91.32	105.41	131.95	153.97
16	22.98	34.17	90.91	170.48	24.03	26.31	20.40	39.32	53.72	75.87	92.83	107.22	134.44	157.11
17	23.43	34.72	92.17	173.53	24.49	26.79	30.92	39.92	54.47	76.90	94.12	108.77	136.56	159.79
18	23.80	35.18	93.21	176.05	24.87	27.19	31.35	40.42	55.08	77.75	95.18	110.04	138.30	162.01

P, percentile; SD, standard deviation; VAT, visceral adipose tissue.

TABLE 4 | VAT-for-age (cm^2) references for girls.

Age (years)	-2 SD	-1SD	1 SD	2 SD	P3	P5	P10	P25	P50	P75	P85	P90	P95	P97
6	14.83	20.56	36.84	47.88	15.44	16.70	18.80	22.75	27.82	33.69	37.20	39.73	43.71	46.45
7	15.15	20.94	42.31	62.16	15.74	16.97	19.08	23.35	29.46	37.52	42.89	47.03	54.07	59.29
8	17.92	24.76	54.25	88.73	18.59	20.02	22.52	27.75	35.68	47.01	55.15	61.79	73.77	83.29
9	19.15	26.40	58.89	99.56	19.85	21.36	24.01	29.59	38.18	50.71	59.91	67.53	81.56	92.95
10	20.90	28.88	63.92	106.31	21.68	23.34	26.26	32.37	41.71	55.21	65.01	73.07	87.74	99.52
11	22.40	31.12	68.38	111.08	23.25	25.07	28.27	34.92	44.98	59.29	69.51	77.80	92.67	104.40
12	22.89	32.03	70.12	111.84	23.79	25.70	29.05	35.99	46.39	60.98	71.25	79.49	94.09	105.44
13	22.81	32.13	70.24	110.56	23.73	25.68	29.09	36.15	46.65	61.21	71.35	79.42	93.58	104.47
14	22.73	32.19	70.38	109.79	23.67	25.65	29.11	36.26	46.85	61.41	71.48	79.44	93.31	103.89
15	22.77	32.38	70.81	109.79	23.72	25.73	29.26	36.50	47.21	61.85	71.91	79.83	93.57	104.00
16	22.87	32.63	71.38	110.18	23.83	25.88	29.46	36.81	47.64	62.38	72.48	80.40	94.09	104.44
17	22.98	32.88	71.93	110.66	23.96	26.04	29.66	37.11	48.05	62.90	73.03	80.97	94.64	104.95
18	23.08	33.09	72.42	111.09	24.07	26.17	29.84	37.37	48.41	63.35	73.52	81.47	95.13	105.42

P, percentile; SD, standard deviation; VAT, visceral adipose tissue.

tissue. In both intra- and inter-observer Bland-Altman plots, greater differences between measurements were noted in VAT groups. However, actual differences in measured adipose tissue areas were up to 2.5 cm^2, which makes this difference almost negligible. The high correlation between observers obtained in our study indicates the reliability of SAT and VAT measurements suggesting that these findings can be used to build models of the percentile charts.

Considering the purpose of our study and pediatric population, we had to change the current MRI image sequence approach which is commonly used for adipose tissue quantification. To date, the majority of published studies have used T1-weighted water-fat sequences (called Dixon sequence). While these sequences have a short acquisition time, the quality of acquired images are strongly dependent on the ability to breath-hold during the examination. The sufficiently long breath-hold is difficult for young children and impossible in case of sedation. Thus, Dixon images of abdomen and pelvis acquired in children are frequently burdened by movement artifacts, making this impossible to evaluate the change in body composition (33). To overcome this limitation, our study used T2-weighted sequences. In the study of Pescatori et al. has shown that the sensitivity and specificity of T1- and T2-weighted sequences in the assessment of adipose tissue are comparable but the results of T2-weighted sequences tended to be more reproducible (32). Furthermore, T2-weighted sequences are included in all standard examination protocols of the abdominal and/or pelvis cavity. Thus, utilizing these sequences for the assessment of SAT and VAT has no major impact on examination and sedation time

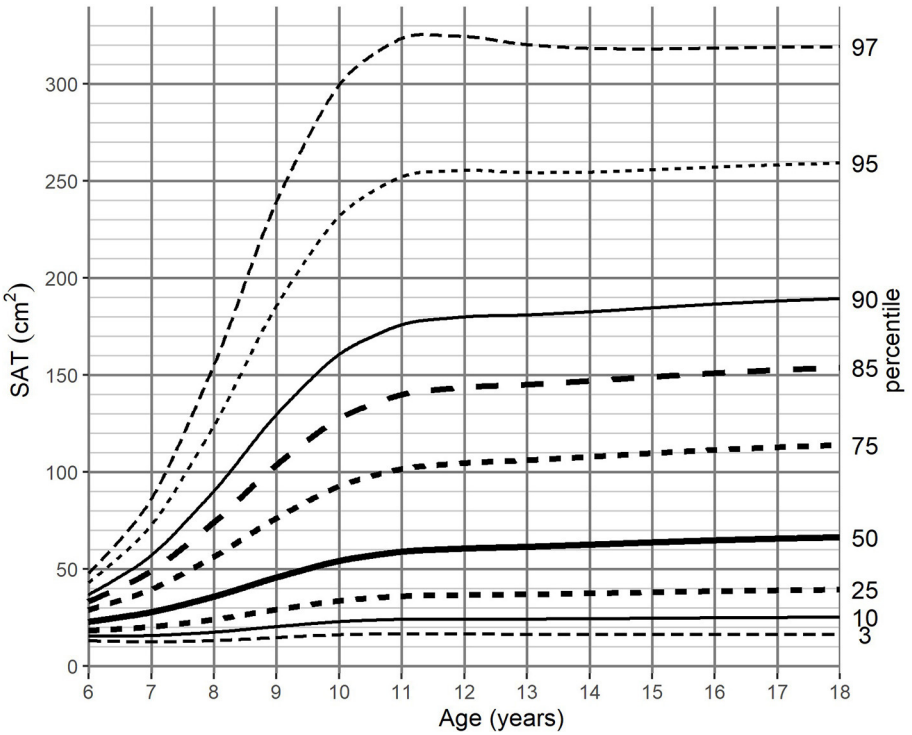

FIGURE 2 | SAT-for-age (cm^2) percentile charts for boys aged from 6 to 18 years. SAT, subcutaneous adipose tissue.

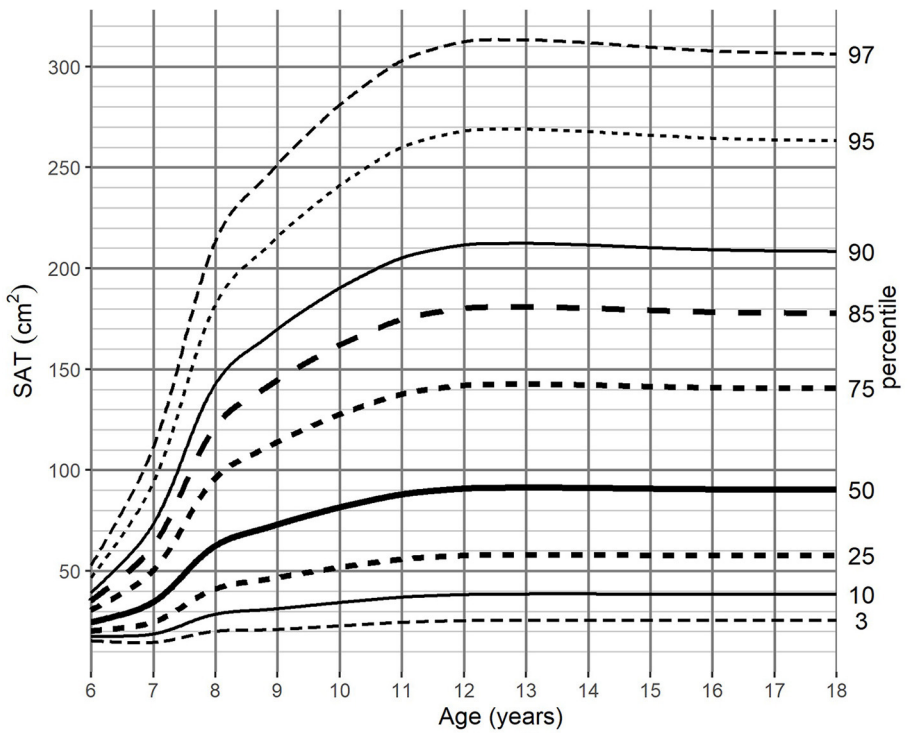

FIGURE 3 | SAT-for-age (cm^2) percentile charts for girls aged from 6 to 18 years. SAT, subcutaneous adipose tissue.

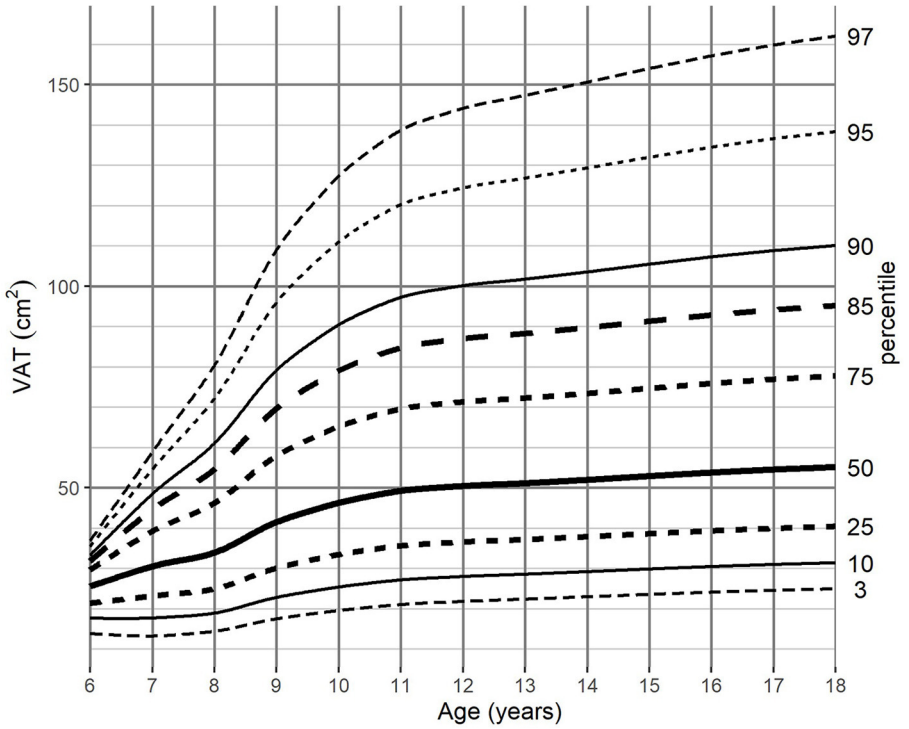

FIGURE 4 | VAT-for-age (cm^2) percentile charts for boys aged from 6 to 18 years. VAT, visceral adipose tissue.

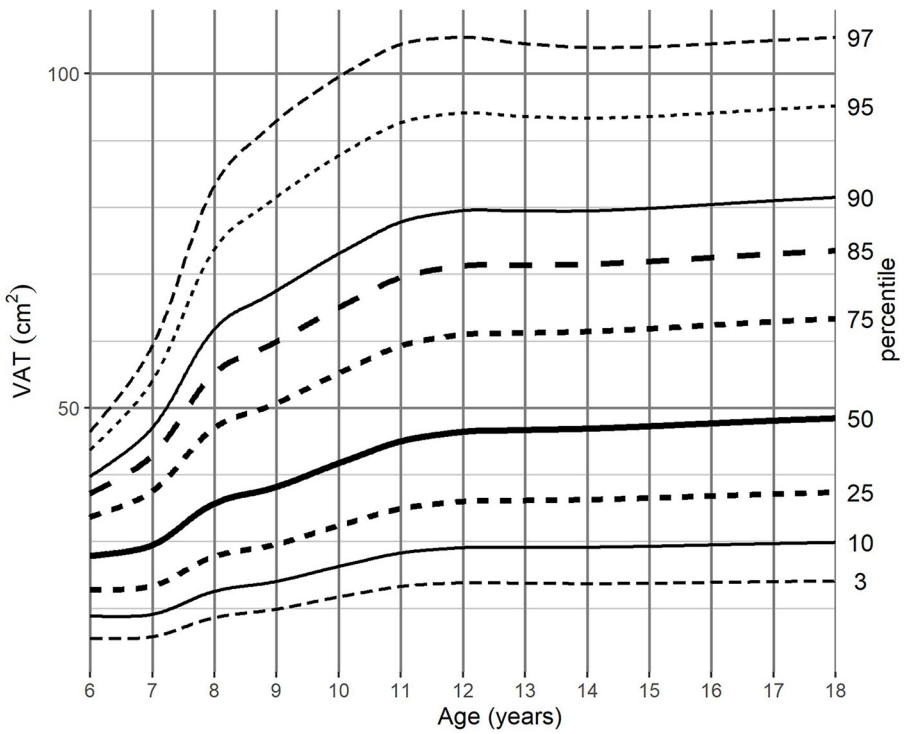

FIGURE 5 | VAT-for-age (cm^2) percentile charts for girls aged from 6 to 18 years. VAT, visceral adipose tissue.

Proper assessment of obtained images requires the involvement of highly qualified personnel. Although tools for manual or semi-automatic SAT and VAT quantification are widely available, segmentation throughout all slices at the level of abdominal or pelvis cavities is time-consuming and impractical (34). Therefore, the quantity of particular adipose tissue depots is usually estimated based on a single cross-section image (18–22, 35, 36). According to the current knowledge, in children cross-sections at the height of L2 vertebrae are the most accurate and correlate to the total amount of SAT and VAT (35, 36). Although in the future artificial intelligence (AI) algorithms may simplify the adipose tissue segmentation process, the current utilization of the single-slice approach is the most optimal solution.

In this context, in the present study by creating the SAT and VAT percentile charts we provide a tool that can be widely and easily implemented in clinical practice. The percentile charts are costless, easy, quick to apply, and enable observation of the growth tendencies over the longer term. The most used percentile charts in pediatric populations are weight, height, and BMI charts (37). However, BMI percentile curves are created by averaging not only SAT and VAT, but also muscle and internal organs mass. As a result, the BMI percentile charts cannot properly illustrate changes in the adipose tissue during children's growth (6, 38). Regardless of gender, the BMI values presented a continuous increase from 6 to 18 years of age both in data presented by WHO (39), as well as in our study. However, only the value of VAT showed a similar upward trend. The SAT surface area stabilized around the age of 12 for both boys and girls. The distribution of BMI standard deviations scores in our population was similar to the regional reference values (40). However, flattening of the BMI curves in the age range from 8 to 10 years in both sexes was noticeable which may be related to the size of our study group.

It should be emphasized that in the same age range, in the contrary to BMI, the SAT, and VAT percentile curves showed a continuous increase. These findings may indicate that our method is more sensitive and precise at reflecting the actual changes in the amount and distribution of body fat.

In our study, data from children with known disorders affecting growth were excluded. The presented standard deviation scores and percentiles should be considered as growth references (not growth standards according to the WHO terminology) because we did not identify environmental conditions "likely to favor the achievement of children's full genetic growth potential" (25). To better monitor, the growing problem of overweight and obesity among children and adolescents in the recommendations of the pediatric obesity experts committee the cut-off values have been determined at the level of 85th and 95th percentiles as the best equivalents of adults' 25th and 30th BMI values (41). Similarly, in our study for the SAT and VAT percentile charts, we proposed the 85th and 95th percentile curves as warning points, above which attention for overweight is required. Determining the exact percentile cut-off for SAT and VAT overweight and obesity requires further research on a larger population.

This study has several limitations. Firstly, the number of participants was relatively small, as percentile charts are usually created during population-based prospective studies. Our study was conducted at a single-center, therefore our results only refer to the Caucasian population. Additionally, semi-automatic adipose tissue assessment is time-consuming and further research on a larger study group would require the implementation of fully automatic tools based on AI deep learning algorithms. Further limitation of this study is the lack of centile charts for children from birth to 5 years of age. Since percentile charts for the youngest children are commonly presented in monthly intervals, our study did not include a sufficient number of healthy participants in these age groups to obtain reliable results.

In conclusion, for the first time, we have shown reference values of SAT and VAT in form of percentile charts for boys and girls during childhood and adolescence. Frequent utilization of MRI examinations in the pediatric population may enable the implementation of our method in clinical practice for body composition assessment and proper nutritional support. In the view of the rapid development of AI deep learning algorithms, there seems to be a high possibility of automatization and incorporation of MRI-based adipose tissue assessment into standard diagnostic protocols.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the need of agreement from University Clinical Center of Gdańsk. Requests to access the datasets should be directed to mleszczynska@uck.gda.pl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KM and MP contributed to the conception or design of the work and drafted the manuscript. KM, WB, MG, MK, PB, DK, and MP contributed to the acquisition, analysis, or interpretation of data for the work. DS, WB, DK, and MG critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.757274/full#supplementary-material

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Comparison of Biochemical and Pathological Parameters and Parenteral Nutrition of ICU Patients Under Supervision of Dietitians and Surgeons

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Background: Nutrient imbalance can frequently occur in patients with indications for parenteral nutrition (PN) after gastrointestinal surgery. This study aimed to compare the recommendations of a surgeon to those of a dietitian in the field of parenteral nutrition.

Methods: This study was performed on 256 patients undergoing gastrointestinal surgery who received PN, which included 120 patients who received PN based on recommendations of the surgeons and 136 patients who were referred to receive PN under the supervision of a dietitian in Razi Hospital in Rasht, Iran. Data on PN and clinical outcomes of the patients were collected.

Results: Patients under the supervision of dietitians received higher vitamin B complex and lipids and lower vitamin A and vitamin E than the surgeon-supervised patients (all $P < 0.001$). In the group receiving PN under the supervision of a surgeon, the level of blood glucose (207 vs. 182, $P < 0.01$), sodium (138 vs. 136, $P = 0.01$), potassium (3.97 vs. 3.53, $P < 0.01$), and white blood cell count (9.83 vs. 9.28, $P < 0.01$) increased significantly at the end of the PN compared to baseline. In the group receiving PN under the supervision of a dietician, the level of serum Cr (1.23 vs. 1.32, $P = 0.04$), Mg (2.07 vs. 1.84, $P < 0.01$), and pH (7.45 vs. 7.5, $P = 0.03$) significantly improved after receiving parenteral nutrition compared to baseline.

Conclusion: The amounts of nutrients recommended for PN by the surgeon and dietitian were different. Implementation of dietitian recommendations in critically ill patients under PN can improve patients' clinical parameters.

Keywords: parenteral nutrition, dietitian, ICU patient, ICU, PN, total parenteral nutrition, surgeon, critically ill patients

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INTRODUCTION

Parenteral Nutrition (PN) is applied as a method of nutrition therapy for ICU patients when bowel failure prevents adequate oral or enteral nutrition (1). After the patient is admitted to the ICU and the patient does not tolerate enteral nutrition for more than 2–3 days, it is recommended to start PN as an alternative or supplemental diet therapy (2). By preventing malnutrition and reducing stress, PN has positive effects on critical care, especially of people older than 50 years of age (3). On average, ∼34,000 patients in the United States receive PN each year. (4). Parenteral nutrition can lead to a moderate increase in pre-albumin, which is one of the markers of survival in critically ill patients (5, 6). However, PN is an expensive nutritional support and may have serious side effects if not properly administered (1). As a result, it is important to provide nutritional recommendations based on standard guidelines in order to minimize nutritional complications. The American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) formed special groups to encourage proper use of PN to promote benefits and reduce risks (1). PN standardization was developed by ESPEN and ASPEN to increase patient safety and clinical suitability (7).

Nutrient imbalance can frequently occur in patients after gastrointestinal surgery with indications for PN (8). Energy-protein deficiency is a common clinical problem in critically ill patients. On the other hand, the risk of overfeeding in parenteral nutrition is greater than that of enteral nutrition (2), and there is a risk of circulatory infection with increasing calorie supply in parenteral nutrition (9) The prevalence of carbohydrate metabolism disorders in critically ill patients is very high, which complicates insulin therapy and the amount of metabolic control achieved (10). High levels of blood glucose in patients with PN can lead to increased mortality (11). Parenteral nutrition can also exacerbate liver and biliary disorders (12).

Surgeons, internists, critical care medicine specialists, pharmacists, and dietitians are responsible for providing nutritional recommendations for ICU patients with PN. Dietitians may apply different nutritional recommendations compared with the other specialists based on different training and responsibilities. Applying the advice of dietitians to assess nutritional requirements and determine the amount of nutritional supplements needed can be effective in improving the health status of critically ill patients. However, some surgeons prefer to order nutritional recommendations directly and not all patients with PN indications are referred to a dietitian. No study has been done to compare the nutritional recommendations of the dietitians with surgeons and their effects on patients. So, the aim of this study was to compare the biochemical and pathological parameters and parenteral nutrition of ICU patients under supervision of surgeons or a dietician.

METHODS

Participants

This retrospective study was performed on 256 patients with Gastroenterologic disease undergoing gastrointestinal surgery with intestinal failure and indication for TPN, which included 120 patients who received PN based on recommendations of the surgeons and 136 patients who received PN under the supervision of a single dietitian in the years 2019 and 2020 in Razi Hospital in Rasht, Iran. The sample size was estimated based on a previous similar study (13). Inclusion criteria were indication for receiving PN, age between 50 and 80 years, and consent to participate in the study. The exclusion criteria were lack of access to sufficient information on the amount of PN received and receiving enteral or oral nutrition along with PN.

Data Collection

Age, sex, weight, height, BMI, duration of hospitalization, medical history including chronic diseases (i.e., diabetes, chronic kidney diseases, hyperlipidemia, and hypertension), diagnosed disease, pathological indices, the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II), Glasgow coma score (GCS), and blood glucose (BG), sodium (Na), potassium (K), urea nitrogen (BUN), creatinine (Cr), white blood cell count (WBC), magnesium (Mg), albumin (Alb), calcium (Ca), and pH were extracted from the medical records before and after TPN. Information related to the nutritional recommendations in the field of TPN, including the amount and percentage of dextrose, amino acids, lipids, vitamins, and minerals were collected from ICU sheets after PN was finished. SMOFlipid® (Fresenius Kabi, United states) was used as the lipid source, which is a composite parenteral nutrition (PN) lipid, comprised of soybean oil (30%), medium-chain triglycerides (MTCs, 30%), olive oil (25%), and fish oil (15%). The mean essential fatty acid content of SMOFlipid is 35 mg/mL (range of 28 to 50 mg/mL) linoleic acid (omega-6) and 4.5 mg/mL (range of 3–7 mg/mL) α-linolenic acid (omega-3) (14). The amount of macro-nutrients administration was determined according to the patient's weight. The amount of micro-nutrients prescribed was vitamin A 50,000 IU/d, vitamin E 100 IU/d, vitamin C 500 mg/d, vitamin B complex containing vitamin B1 10 mg/d, vitamin B2 4 mg/d, vitamin B3 40 mg/d, vitamin B5 6 mg/d, and vitamin B6 4 mg/d.

Statistical Analysis

The two groups receiving parenteral nutrition under the supervision of surgeons or a dietitian were compared in terms of demographic and pathological indicators using independent *T*-test and Chi-square methods. Also, the amounts of macronutrients and micronutrients received in the two groups were compared by independent *T*-test. The two groups were compared regarding the number of patients who received the nutrients using Chi-square and Fisher's exact test. The values of clinical and biochemical parameters before and after PN in each group were compared by paired *t*-test. All analyzes were performed using SPSS software version 21 and the significance level was considered as $P > 0.05$.

Ethical Considerations

Written consent forms were obtained from all participants or their first-degree relatives. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.) code IR.SBMU.CRC.REC.1398.015).

TABLE 1 | Characteristics of the patients.

	Surgeon-supervised patients ($n = 120$)	Dietitian -supervised patients ($n = 136$)	*P*
Males	56 (46.7%)	68 (50.0%)	0.49
Females	64 (53.3%)	68 (50%)	
Age (y)	62 (±12)	67 (±18)	0.28
Underlying diseases			
HTN	56 (47%)	68 (50%)	0.49
HLP	16 (13%)	32 (23.5%)	0.24
IHD	8 (6.7%)	12 (8.8%)	0.56
DM	28 (23.3%)	84 (61.8%)	0.002
CKD	0 (0%)	15 (20%)	0.03
Hospitalization (day)	22 (±8)	27 (±31)	0.32
Weight (kg)	75 (±7)	73 (±6)	0.31
Height (cm)	168 (±6)	165 (±6)	0.11
APACHE II	21 (±1)	14 (±2)	<0.001
GCS	15 (± 1,5)	8 (±0.5)	<0.001
BG (mg/dl)	182 (±28)	209 (±31)	0.001
NA (mEq/L)	135 (±3)	141 (±5)	<0.001
K (mEq/L)	3 (±0.3)	4 (±0.4)	<0.001
BUN (mg/dl)	38 (±10)	47 (±14)	0.004
Cr (mg/dl)	1.11 (±0.1)	1.32 (±0.2)	<0.001
Hb (gr/dl)	9.51 (±1)	8.98 (±1)	0.06
BMI (kg/m^2)	26 (±3)	27 (±2.7)	0.85

HTN, hypertension; HLP, hyperlipoproteinemia; IHD, ischemic heart disease; DM, diabetes mellitus; CKD, chronic kidney disease; APACH II, The Acute Physiologic Assessment and Chronic Health Evaluation II; GCS, Glasgow coma score; BG, blood glucose; Na, sodium; K, potassium; BUN, blood urea nitrogen; Cr, creatinine; Hb, hemoglobin; BMI, body mass index.

RESULTS

No significant difference was found in terms of sex (males: 46.7 vs. 50.0%), age (62 ± 12 vs. 67 ± 18 years), weight (73 ± 6 vs. 75 ± 7 kg), height (165 ± 6 vs. 168 ± 6 cm), duration of hospitalization (27 ± 31 vs. 22 ± 8 days), and BMI (27 ± 2.7 vs. 26 ± 3 kg/m^2) between dietitian-supervised and surgeon supervised groups (**Table 1**). In addition, no significant difference was seen between the two groups in terms of history of hypertension (50 vs. 47%), hyperlipidemia (23.5 vs. 13%), ischemic heart disease (8.8 vs. 6.7%), and hemoglobin level (9 ± 1 vs. 9 ± 1) (**Table 1**).

Dietitian-supervised patients had a higher burden of chronic diseases (79.4 vs. 53.3%, $p = 0.025$), diabetes (61.8 vs. 23.3%, $P = 0.002$), chronic kidney disease (CKD) (20 vs. 0%, $P = 0.03$), and levels of BG (209 ± 31 vs. 182 ± 28 mg/dl, $P = 0.001$), Na (141 ± 5 vs. 135 ± 3 mEq/L, $P < 0.001$), K (4 ± 0.4 vs. 3 ± 0.3 mEq/L, $P < 0.001$), BUN (47 ± 14 vs. 38 ± 10 mg/dl, $P = 0.004$), and Cr (1.32 ± 0.2 vs. 1.11 ± 0.1 mg/dl, $P < 0.001$) compared to the surgeon-supervised patients. Surgeon-supervised patients had higher APACHE II score (21 ± 1 vs. 14 ± 2, $P < 0.001$) and GCS (15 vs. 8 ± 0.5, $P < 0.001$) compared to the dietitian-supervised patients.

Regarding the percentages of the patients who received different nutrients and met the recommended amounts, the results showed that the number of patients receiving lipid ($P < 0.001$) and vitamin B complex was significantly higher in dietitian-supervised group, while the number of patients receiving vitamin A and vitamin E was significantly higher in surgeon-supervised group (**Table 2**). Regarding nutritional recommendations, the number of days that each patient received lipids (5.59 ± 1.13 vs. 2 ± 2.55 days, $P < 0.001$) and vitamin B complex (8.1 ± 2.8 vs. 0 days, $P = 0.001$) was higher in the dietitian-supervised group compared to the surgeon-supervised group (**Table 2**).

In the group receiving parenteral nutrition under the supervision of a surgeon, the level of BG (207 ± 35 vs. 182 ± 28, $P < 0.01$), sodium (138 ± 3 vs. 136 ± 3 mg/dl, $P = 0.01$), potassium (3.97 ± 0.4 vs. 3.53 ± 0.4, $P < 0.01$), and white blood cell count (9.83 ± 2.5 vs. 9.28 ± 2.4 10^9/L, $P < 0.01$) increased significantly at the end of the parenteral nutrition period compared to baseline. In the group receiving parenteral nutrition under the supervision of a dietician, the level of serum Cr (1.23 ± 0.2 vs. 1.32 ± 0.2 mg/dl, $P = 0.04$), Mg (2.07 ± 0.2 vs. 1.84 ± 0.2 mg/dl, $P < 0.01$), and pH (7.45 vs. 7.5, $P = 0.03$) significantly improved after receiving parenteral nutrition compared to baseline. Serum urea, albumin and calcium levels after parenteral nutrition in the two groups were not significantly different from the baseline levels (**Table 3**).

DISCUSSION

In the present study, for the first time, the performance of dietitians was compared to surgeons in parenteral feeding of patients after gastrointestinal surgery. The results indicated that patients with worsening conditions were referred to a dietitian. Moreover, patients under the supervision of dietitians received higher vitamin B complex and lipids than the group under the

TABLE 2 | Average number of days to receive nutrients and the percentages of the patients who received nutrients among patients under surgeon and dietitian recommendations.

	Number of days to receive nutrients			Percentages of the patients who received nutrients		
	Surgeon-supervised patients ($n = 120$)	Dietitian -supervised patients ($n = 136$)	*P*	Surgeon-supervised patients ($n = 120$)	Dietitian -supervised patients ($n = 136$)	*P*
Dextrose	5.27 (±0.944)	5.45 (±0.850)	0.42	116 (96.7%)	124 (91.2%)	0.36
Amino acid	5.28 (±0.960)	5.44 (±0.824)	0.47	116 (96.7%)	136 (100%)	0.47
Lipid	2 (±2.54613)	5.59 (±1.13131)	<0.001	48 (40%)	136 (100%)	<0.001
Vitamin B complex	0 (±0)	8.1 (±2.82517)	0.001	0 (0%)	120 (88.2%)	<0.001
Vitamin C	8.33 (±2.510)	8.26 (±2.863)	0.91	120 (100%)	124 (91.2%)	0.14
Vitamin A	8.17 (±2.674)	7.83 (±5.154)	0.88	116 (96.7%)	20 (14.7%)	<0.001
Vitamin E	8.20 (±2.631)	7.50 (±9.192)	0.93	120 (100%)	8 (5.9%)	<0.001

TABLE 3 | Comparison of Clinical outcomes of two groups at baseline and after parenteral nutrition.

	Surgeon-supervised patients ($n = 120$)				Dietitian -supervised patients ($n = 136$)			
	Mean (±SD) at baseline	Mean (SD) after PN	Mean difference	*P*	Mean (SD) at baseline	Mean (SD) after PN	Mean difference	*P*
BG (mg/dl)	182 (±28.35)	207 (±35.46)	24.29	<0.01	209 (±31.25)	208 (±43.57)	−1.94	0.81
Na (mEq/L)	136.6 (±3.1)	138.2 (±3.85)	1.6	0.01	141.79 (±5.03)	142.02 (±4.96)	0.23	0.77
K (mEq/L)	3.53 (±0.37)	3.97 (±0.41)	0.43	<0.01	3.98 (±0.45)	4.1 (±0.38)	0.11	0.23
BUN (mg/dl)	37.86 (±9.86)	36.86 (±9.53)	1	0.36	46.94 (±13.96)	44.85 (±13.75)	−2.08	0.31
Cr (mg/dl)	1.11 (±0.11)	1.31 (±0.17)	0.01	0.48	1.32 (±0.24)	1.23 (±0.23)	−0.09	0.04
WBC (109/L)	9.28 (±2.37)	9.83 (±2.55)	0.55	<0.01	8.71 (±2.46)	9.1 (±2.97)	0.38	0.14
Mg (mg/dl)	1.95 (±0.25)	1.98 (±0.21)	0.03	0.31	1.84 (±0.15)	2.07 (±0.22)	0.22	<0.01
Alb (g/dl)	2.97 (±0.31)	2.88 (±0.17)	−0.04	0.49	2.93 (±0.31)	2.89 (±0.28)	−0.04	0.49
Ca (mg/dL)	8.45 (±0.45)	8.38 (±0.64)	−0.7	0.42	7.75 (±0.45)	7.85 (±0.64)	0.1	0.45
pH	7.44 (±0.86)	7.45 (±0.73)	0.01	0.08	7.5 (±0.86)	7.45 (±0.73)	−0.05	0.03

supervision of surgeons. In the surgeon-supervised group, the patients received higher amounts of vitamin A and vitamin E than the dietitian-supervised patients. In the group receiving parenteral nutrition under the supervision of a surgeon, the level of BG, sodium, potassium, and white blood cells count increased significantly at the end of the PN compared to baseline. In the group receiving PN under the supervision of a dietician, the level of serum Cr, Mg, and pH significantly improved after receiving parenteral nutrition compared to baseline.

Providing parenteral nutrition can be vital for patients with intestinal failure, but achieving the desired amount and balance is a complicated issue and many factors such as age, degree of inflammation, number of failing organs, comorbidities, estimated length of stay, gastrointestinal function, fluids and electrolytes, and BG control must be considered in parenteral nutrition planning. Patients admitted to the ICU should receive PN within 24–48 h if they are unable to tolerate enteral nutrition.

Tignanelli et al. reported that mortality was lower in patients with nutritional counseling and that malnutrition should be prevented in order to prevent adverse consequences. Malnutrition increases the risk of disease, adverse surgical outcomes, length of stay in the hospital, and cost burden. Disease-induced stress in ICU patients may accelerate the development of malnutrition.

Patients receiving nutritional care from dietitians were reported to reach the target dietary intake faster and their clinical outcomes were improved (15). Vankrunkelsven et al. examined parenteral administration of micronutrients including phosphate, magnesium, iron and B-complex vitamins including vitamins B12, B1, and folic acid and concluded that nutrient deficiency may be related to the degree of inflammation (16).

In the study by Heyland et al., most ICU patients did not receive adequate nutritional support, especially early in their illness, and their energy and protein requirements were not correctly estimated (17).

We found that patients receiving parenteral nutrition under the supervision of a dietitian received similar dextrose compared with the patients under the supervision of a surgeon. Several previous reports indicated that receiving dextrose parenterally during the first week in the ICU leads to fewer secondary infections, less weakness, rapid recovery, and reduced patient mortality (18–21). However, hyperglycemia is an independent risk factor for short-term infection in patients undergoing surgery (14, 15). The risk of hyperglycemia as a part of the endocrine metabolic response to stress is present in almost all patients in the ICU. If the requirement for intravenous dextrose in patients is not specifically assessed and determined, it may increase the risk of hyperglycemia. In the present study, the blood sugar level of patients under the supervision of a surgeon increased significantly after receiving intravenous nutrition.

In the present study, patients receiving parenteral nutrition under the supervision of a dietitian received more lipid than

patients under the supervision of a surgeon. Lipids should be considered as an integral part of PN to provide energy and ensure a supply of essential fatty acids. Providing essential fatty acids in PN using standard lipid emulsions can lead to additional clinical benefits such as reductions in both infection rate and length of hospital stay (22, 23). Various mixtures of lipid emulsions, including soybean oil, medium chain triglycerides, olive oil, and omega-3 rich fish oil, are widely available for parenteral nutrition. Omega-3 fatty acids can have beneficial immune-regulating and anti-inflammatory effects in a wide range of patients undergoing surgery (23). The addition of EPA and DHA to lipid emulsions may improve cell membrane function and inflammation, and reducing the length of stay of critically ill patients in the ICU (23). Pradelli et al. in a systematic review reported that omega-3 fatty acid-containing PN was associated with clinically significant improvement in patient outcomes (24). In the present study, SMOFlipid was used as the lipid source of TPN, which is rich in omega-3 fatty acids and higher lipid intake in the group under the supervision of a dietitian was associated with improved serum creatinine and pH levels and no increase in BG levels. However, high intake of unsaturated fatty acids in critically ill patients may be associated with side effects such as disturbed liver function or altered balances of antioxidants (25) and should be recommended according to the patient's requirements.

The results of this study indicated that dietitians may be better able to assess the nutritional requirements of critically ill patients and significantly help to improve the biochemical and pathological parameters of these patients. In line with the present study, evidence suggests that dietitians are key members of the ICU care team who can help improve patient outcomes (26). Severely ill patients who had sufficient nutritional intake were less likely to develop pneumonia, pulmonary insufficiency, gastrointestinal bleeding, or the need for mechanical ventilation (27).

The intake of vitamins A and E in the group under the supervision of the surgeon was higher and the intake of B vitamins was lower than the group under the supervision of the dietitian. Because of the risk of toxicity, fat soluble vitamins such as vitamin E and vitamin A should not be prescribed at high doses without proven deficiency. It was reported that patients with renal failure may be at risk for symptomatic vitamin A toxicity if given PN with standard retinol supplementation. However, vitamin E may reduce the length of mechanical ventilation in ICU patients (28, 29). On the other hand, critical illness in adults is characterized by absolute or relative thiamine depletion, which is associated with an almost 50% increase in mortality. Vitamin B1 is likely to be used in high-risk patients to prevent Wernicke's encephalopathy and heart failure. Moreover, administration of vitamin B1 may be used as adjunctive therapy in septic shock (30–33).

However, this study was limited to the ICU patients undergoing surgery, which makes it difficult to generalize the results to other patients. Moreover, the dietitian-supervised patients were significantly different compared with surgeon-supervised patients in terms of history of chronic diseases and pathological and biochemical parameters which may influence nutritional recommendations as well as the biochemical changes observed after TPN. In addition, individual dietary requirements of the patients were not assessed. Future longitudinal studies are needed to confirm these results and to investigate the effects of dietitian and surgeon PN recommendations on health outcomes of the patients.

CONCLUSION

The results indicated that patients with worsening conditions were referred to a dietitian. Moreover, patients under the supervision of dietitians received higher vitamin B complex and lipids than the surgeon-supervised patients. In the surgeon-supervised group, the patients received higher amounts of vitamin A and vitamin E than the dietitian-supervised patient. Biochemical changes suggestive of better outcomes were observed in the dietician-supervised group. Future longitudinal studies are needed to investigate the effects of dietitian and surgeon PN recommendations on health outcomes of the patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The written consent forms were obtained from all participants or their first-degree relatives. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (code IR.SBMU.CRC.REC.1398.015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SD, MB, MA, MG, SR, SG, AH, and NM designed the study, involved in the data collection, analysis, and drafting of the manuscript. SMD, MOG, and SD were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Prevalence and Prognostic Value of Malnutrition Among Elderly Cancer Patients Using Three Scoring Systems

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Background: Malnutrition is common in patients with cancer and is associated with adverse outcomes, but few data exist in elderly patients. The aim of this study was to report the prevalence of malnutrition using three different scoring systems and to examine the possible clinical relationship and prognostic consequence of malnutrition in elderly patients with cancer.

Methods: Nutritional status was assessed by using controlling nutritional status (CONUT), the prognostic nutritional index (PNI), and the nutritional risk index (NRI). Quality-of-life (Qol) was assessed during admission by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30. Performance status (PS) was assessed by using the Eastern Cooperative Oncology Group (ECOG) classification. The relationship between nutritional status and overall survival and Qol were examined.

Results: Data were available for 1,494 elderly patients with cancer (63.65% male), the mean age was 70.76 years. According to the CONUT, NRI, and PNI, 55.02, 58.70, and 11.65% patients were diagnosed with malnutrition, respectively. Worse nutritional status was related to older, lower BMI, lower hand grip strength, and more advanced tumor stage. All malnutrition indexes were correlated with each other (CONUT vs. PNI, $r = -0.657$; CONUT vs. NRI scores, $r = -0.672$; PNI vs. NRI scores, $r = 0.716$, all $P < 0.001$). During a median follow-up of 43.1 months, 692 (46.32%) patients died. For patients malnourished, the incidence rate (events-per-1,000person-years) was as follows: CONUT (254.18), PNI (429.91), and NRI (261.87). Malnutrition was associated

with increased risk for all-cause mortality (adjust HR [95%CI] for CONUT: 1.09 [1.05–1.13], $P < 0.001$; PNI: 0.98[0.97–0.99], $P < 0.001$; NRI: 0.98 [0.98–0.99], $P < 0.001$). All malnutrition indexes improved the predictive ability of the TNM classification system for all-cause mortality. Deterioration of nutritional status was associated with deterioration in QoI parameters and immunotherapeutic response ($P < 0.001$).

Conclusions: Malnutrition was prevalent in elderly patients with cancer, regardless of the assessment tools used, and associated with lower QoI and the immunotherapy response.

Keywords: elderly patients, malnutrition index, cancer, prognostic, NRI

INTRODUCTION

Cancer is a devastating disease characterized by a poor prognosis, mainly in elderly patients. Clinical interventions for cancer have changed significantly in the past years. Although treatment options for patients with cancer have increased in the recent past, the prognosis remains relatively poor for elderly cancer patients. Malnutrition is common in elderly cancer patients; however, it is commonly ignored in routine clinical care (1). Changes in nutritional status and/or deterioration of the performance status (PS) are correlated with increased risk of acute toxicity, reduced therapy response, and shorter survival following anticancer treatment (2). Several studies have reported the importance of the nutritional status in elderly patients with cancer. Identifying high-risk patients based on modifiable clinical characteristics, such as nutritional status, is essential to recommend interventions targeting these variables to improve clinical outcomes and reduce health costs (2).

A previous study reports that malnutrition is an impairment poor prognostic factor in elderly patients with cancer (3). The death of several patients with cancer can be attributed to malnutrition rather than cancer itself (4). Malnutrition is an important factor in anticancer treatment and is reported in patients with various body weights and body mass indexes (BMI), independent from adiposity (5). Malnutrition can easily be alleviated; thus physicians can effectively manage it in various diseases (6). Screening patients with cancer for malnutrition can identify patients who can benefit from tailored intervention to prevent and treat malnutrition, improve prognosis and the quality of life (Qol) (7). European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines recommend that all patients should be screened regularly for the presence or risk of malnutrition (8). Several malnutrition scoring indexes have been developed to evaluate immunocompetence and nutritional conditions for patients, such as the controlling nutritional status (CONUT) index (9), the prognostic nutritional index (PNI), and the nutritional risk index (NRI). Data obtained using these malnutrition indexes are quantitative and can be obtained by routine blood testing in various institutions.

Currently, findings on the interaction between these assessment tools and their comparative use for the prediction of clinical outcomes in elderly patients with cancer are limited. The prevalence of malnutrition varies depending on the assessment tools used. The aim of the present study was to explore the prevalence of malnutrition using three different scoring systems and to evaluate the possible clinical relationship and prognostic value of malnutrition in elderly cancer patients.

METHOD AND PARTICIPANTS

Study Population

This is a prospective cohort study based on the investigation on nutrition status and its clinical outcome of common cancers (INSCOC) cohort in China. The trial was registered at http://www.chictr.org.cn under the registration number ChiCTR1800020329. Data were collected prospectively from multicenter across China. The design, methods, and development of the INSCOC study were as described previously (10, 11). All patients included in the INSCOC cohort were diagnosed with solid tumors and were 18 yr old or older. Patients were examined through a survey before undergoing cancer treatment (surgery, chemotherapy, radiotherapy, or other treatments). Participants were enrolled in this cohort as only inpatients, requiring an inpatient stay >48 h. Patients who could not communicate and/or were unable to provide verbal consent were excluded from the study. The study was conducted following the principles outlined in the Declaration of Helsinki and was approved by the ethical committee from each local center. Written/verbal informed consent for using clinical data without revealing personal information was obtained from all participants. Patients aged 65 years or older were included in the current secondary analysis. Patients who had no records of height, weight, scrum albumin, cholesterol, or lymphocyte count were excluded from the study. Patients with clinical evidence of active infection and the presence of immunologic disease were also excluded from the study. No patient had suspected or documented bone marrow involvement. A flow diagram for study subject screening and grouping is shown in **Supplementary Figure 1**.

Demographics and Clinical Characteristics

Data on age, sex, primary cancer type, and tumor stage were obtained from the electronic medical record system. Body mass index (BMI), defined as the weight (kilograms) divided by the square of height (meters), was calculated for all patients. Patients were classified into four groups including underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight

TABLE 1 | Baseline characteristics of the study population.

Characteristics	Overall $n = 1,494$
Demographic data	
Age, years	70.76 (5.16)
Gender, male	951(63.65%)
BMI, kg/m^2	22.58 (3.55)
Smoking, yes	696 (46.59%)
Alcohol, yes	289 (19.34%)
Comorbidities	
Absent	1,081 (72.36%)
Hypertension	337 (22.56%)
Others	76 (5.09%)
Disease data	
Tumor location	
Lung	458 (30.66%)
Digestive	759 (50.80%)
Other	277 (18.54%)
Tumor stage:	
I	147 (9.84%)
II	336 (22.49%)
III	373 (24.97%)
IV	638 (42.70%)
Chemotherapy, yes	939 (62.85%)
Radiotherapy, yes	1,494(100.00%)
Immunotherapy, yes	109 (7.30%)
Surgery, yes	357 (23.90%)
ECOG	1.09 (0.80)
Laboratory data	
Albumin, g/dl	3.80 (0.53)
Cholesterol, mg/dl	182.95 (60.94)
Lymphocyte, *10^9/L	1.67 (1.37)
Nutritional data	
CONUT, as continuous	2.30 (2.21)
Category	
Absent	672 (44.98%)
Mild	602 (40.29%)
Moderate	193 (12.92%)
Severe	27 (1.81%)
PNI, as continuous	46.05 (9.90)
Category	
Absent	1,320 (88.35%)
Moderate	77 (5.15%)
Severe	97 (6.49%)
NRI, as continuous	96.96 (10.32)
Category	
Absent	617 (41.30%)
Mild	174 (11.65%)
Moderate	607 (40.63%)
Severe	96 (6.43%)
PG-SGA, as continuous	6.26 (4.48)
Category	
Absent	52 (3.48%)
Mild	503 (33.67%)
Moderate	549 (36.75%)
Severe	390 (26.10%)
HGS, kg	22.38 (8.93)
EORTCQLQ-C30	39.21 (4.79)
PN, yes	188 (12.58%)
EN, yes	146 (9.77%)

Values are mean (SD) or n (%). BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; CONUT, Controlling Nutritional Status score; PNI, prognostic nutritional index; NRI, nutritional risk index; PG-SGA, a patient-generated subjective global assessment; HGS, handgrip strength; EORTCQLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PN, parenteral nutrition; EN, enteral nutrition.

(24.0–28.0 kg/m^2), and obese (>28 kg/m^2). Chronic disease was defined as any previous history of hypertension, diabetes, chronic obstructive pulmonary disease, and chronic hepatitis, and information on the history of chronic disease was retrieved from the clinical history of the diagnoses recorded in patients notes. The clinical stage of cancer was evaluated by TNM staging based on the 8th AJCC TNM classification system.

Performance status was determined by the Eastern Cooperative Oncology Group (ECOG). Patients were classified in different categories ranging from grade 0 (fully active) to grade 5 (dead). ECOG grade 5 was excluded in the current study. Patient-generated subjective nutrition assessment (PG-SGA) was assessed and recorded by trained staff at baseline. Data on Qol were collected on the day of admission using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTCQLQ-C30 Version 3.0, Qol). The QLQ-C30 scale is a 30-item questionnaire comprising functional assessment (physical, role, emotional, social, and cognitive), symptom assessment (fatigue, nausea and vomiting, and pain), and global health and Qol assessment (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (12). Overall and subscale scores were calculated following specific guidelines (higher scores indicated better Qol).

Malnutrition Assessment

We reassessed the nutritional status (using CONUT, PNI, and NRI) based on the data collected during the baseline. CONUT, PNI, and NRI indexes were calculated using the following formula:

CONUT: includes serum albumin level, total cholesterol level, and lymphocyte count (9); each parameter can be scored as 0, 1, or 2.

PNI: 10*serum albumin (g/dl) + 0.005*total lymphocyte count (mm^3).

NRI: 1.489*serum albumin (g/l) + 41.7* (weight in kilograms/ideal weight).

Venous blood sample (scrum albumin, total lymphocyte count, and cholesterol) was collected on the first day of admission after overnight fasting. All the measurements were

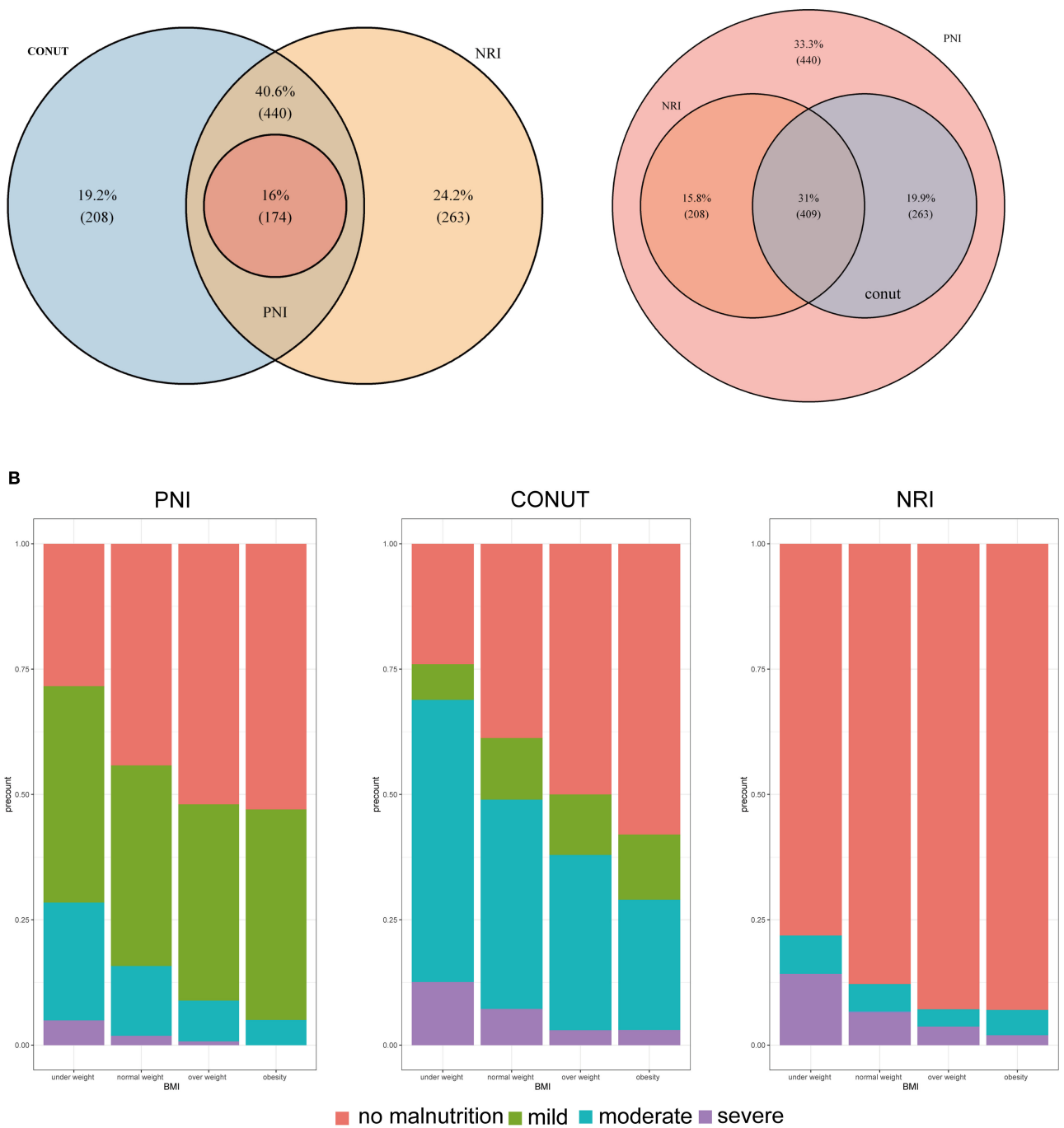

FIGURE 1 | (A) Venn diagram. The numbers reported in each circle indicate the cumulative frequency of malnutrition (any degree [left] vs. no-malnourished [right]) according to each malnutrition index. **(B)** Percentage of malnutrition by subgroups of patients according to body mass index. CONUT: Controlling Nutritional Status score, PNI: prognostic nutritional index, NRI: nutritional risk index.

analyzed at a central laboratory and standardized to avoid differences caused by location and/or scale of measurements between laboratories. Patients were classified into absent, mild (expect PNI), moderate, and severe malnutrition risk based on CONUT, PNI, and NRI indexes as shown in **Supplementary Table 1** (13).

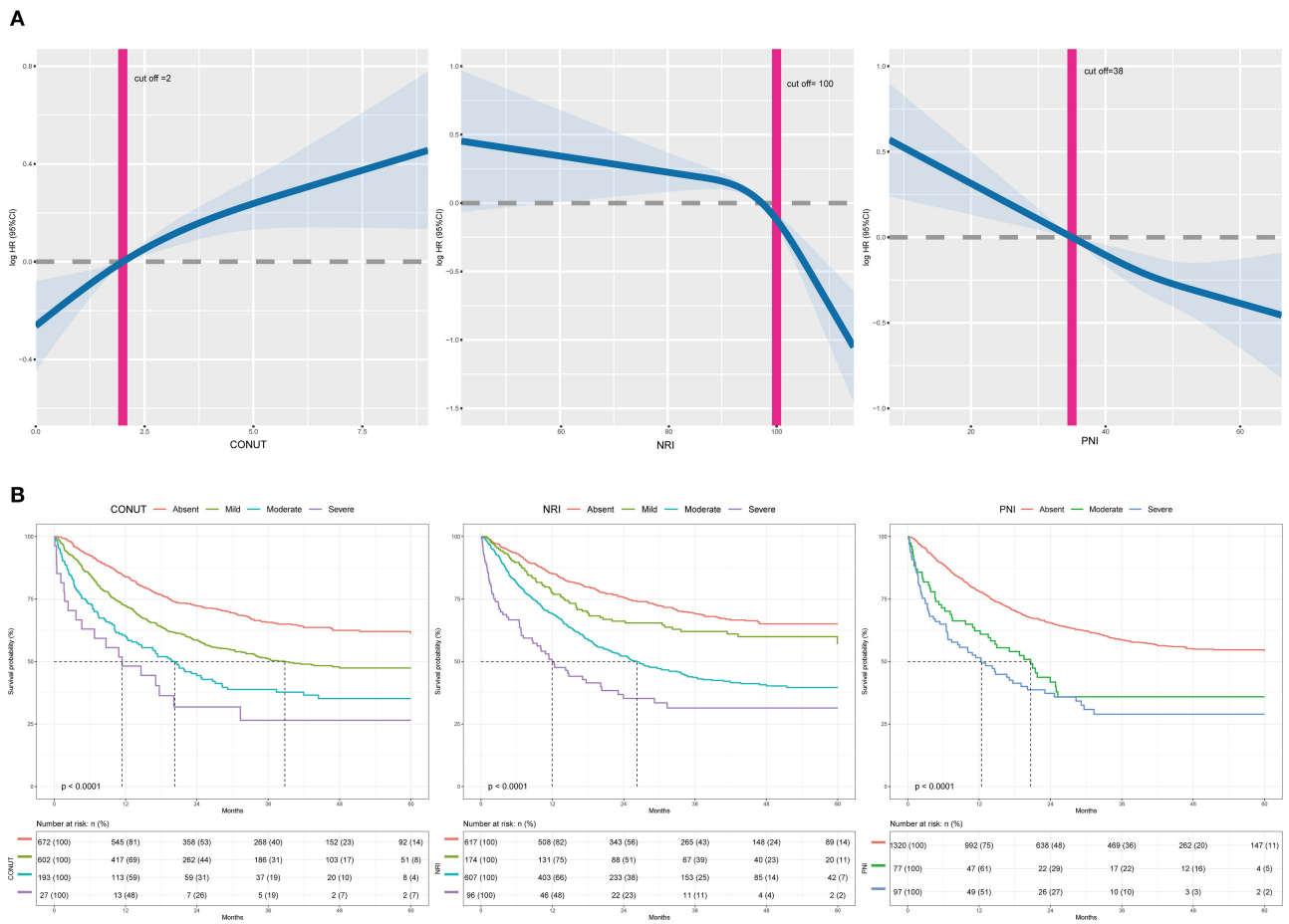

FIGURE 2 | (A) The incidence of all-cause mortality is shown after adjusted for age, gender, BMI, comorbidities disease, smoking, alcohol, tumor location, tumor stage, chemotherapy, immunotherapy, surgery, parenteral nutrition intervention, enteral nutrition intervention, ECOG, handgrip strength, and EORTCQLQ-C30. For NRI, total cholesterol and lymphocyte count were adjusted additionally. For PNI, lymphocyte count was adjusted additionally. The *x*-axis shows the score of each malnutrition index. The curve shows the incidence, with 95% CI, of the estimates. **(B)** Kaplan-Meier curves for all-cause mortality by the category of each malnutrition index in elderly patients with cancer. CONUT, Controlling Nutritional Status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

Outcome and Follow-up

All-cause mortality was the primary endpoint in the current study. Patients were regularly followed up by telephone or outpatient visits to collect information on clinical outcomes. Overall survival was expressed in months and defined as the time from the date of admission until death or censored if alive at follow-up analysis (30 December 2019).

Statistical Analysis

Demographic characteristics of the study population were described. Continuous data were expressed as mean and standard deviation (unless otherwise specified), and categorical data were expressed as a number and percentage (n, %). Independent students *t*-test or non-parametric tests were used to compare differences between groups. Multiple groups were compared by one-way ANOVA with an appropriate *post-hoc* test. Pearson chi-square test or Fisher's exact test was used for comparing proportions between the groups. Correlation between quantitative variables was explored through Pearson's correlation analysis. Venn diagrams were used to illustrate the relationship between the three malnutritional indexes. We selected covariates and potential confounders *a priori*, based on previous scientific knowledge (14). Variable was removed from the model where variables were highly intercorrelated (multicollinearity). Univariate and multivariate COX regression analyses were performed to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs) of significant risk predictors based on over survival. A restricted cubic spline plot was used to explore the shape of the correlation between malnutrition index and clinical outcome. Kaplan–Meier curves and log-rank tests were used to present time-to-event data and compare survival between groups, respectively. Harrell C-index (15), continuous net reclassification improvement **(cNRI)** (16), integrated discrimination improvement **(IDI)** (17), and time–area under the curve (AUC) were calculated to assess and compare the discrimination capacity of the three malnutrition

TABLE 2 | Cox proportional analyses of malnutrition indexes to predict all-cause mortality for elderly patients with cancer.

	Crude HR(95%CI)	*P*-value	Adjusted HR (95% CI)[a]	*P*-value	Adjusted HR(95%CI)[b]	*P*-value
CONUT, as continuous	1.16 (1.12–1.19)	<0.001	1.16 (1.12–1.19)	<0.001	1.09 (1.05–1.13)	<0.001
Category						
Absent	Ref					
Mild	1.64 (1.37–1.95)	<0.001	1.52 (1.28–1.82)	<0.001	1.34 (1.12–1.61)	0.002
Moderate	2.48 (1.97–3.11)	<0.001	2.05 (1.62–2.59)	<0.001	1.72 (1.34–2.20)	<0.001
Severe	3.48 (2.18–5.56)	<0.001	2.85 (1.78–4.58)	<0.001	1.89 (1.14–3.13)	0.014
PNI, as continuous	0.97 (0.96–0.98)	<0.001	0.97 (0.97–0.98)	<0.001	0.98 (0.97–0.99)	<0.001
Category						
Absent	Ref					
Moderate	1.91 (1.41–2.59)	<0.001	1.72 (1.26–2.33)	<0.001	1.60 (1.17–2.19)	0.004
Severe	2.58 (1.99–3.34)	<0.001	2.19 (1.68–2.85)	<0.001	2.08 (1.58–2.73)	<0.001
NRI, as continuous	0.98 (0.97–0.98)	<0.001	0.98 (0.97–0.98)	<0.001	0.98 (0.98–0.99)	<0.001
Category						
Absent	Ref					
Mild	1.34 (1.01–1.78)	0.044	1.29 (0.97–1.71)	0.083	1.29 (0.97–1.71)	0.084
Moderate	2.23 (1.85–2.67)	<0.001	1.98 (1.64–2.38)	<0.001	1.74 (1.44–2.10)	<0.001
Severe	3.70 (2.77–4.95)	<0.001	3.05 (2.26–4.10)	<0.001	2.67 (1.95–3.64)	<0.001

a: Adjusted by age, gender, BMI. b: Adjusted by age, gender, BMI, comorbidities disease, smoking, alcohol, tumor location, tumor stage, chemotherapy, immunotherapy, surgery, parenteral nutrition intervention, enteral nutrition intervention, ECOG, handgrip strength, EORTCQLQ-C30. For NRI, total cholesterol and lymphocyte count were adjusted additionally. For PNI, lymphocyte count was adjusted additionally. HR, hazard ratio; CI, confidence interval; CONUT, Controlling Nutritional Status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

indexes to predict mortality. A two-sided *p*-value of 0.05 was considered statistically significant. All statistical analyses were performed using R, version 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

A total of 1,494 elderly participants diagnosed with cancer were enrolled in the current study. Most patients were male (63.65%), and the mean age was 70.76 years. The prevalence of distant metastases was high (42.70%), and the most common cancer was digestive cancer (50.80%). All patients underwent radiotherapy, and 62.85% of the patients included in this study underwent systemic chemotherapy treatment. Hundred and nine (7.30%)patients received immunotherapy (PD-1/PD-L1). However, patients presented with low mean Qol, as indicated by mean QLQ-C30 score at 39.21 ± 4.79, showed a PS that indicated normal capability with independent daily activities (ECOG: 1.09 ± 0.80). Details on the baseline characteristics of this study are presented in **Table 1**.

Prevalence and Clinical Association of Malnutrition

The proportion of patients with malnutrition varied from 55.02% with the CONUT to 58.70% with the NRI, and 11.65% with the PNI. Analysis using CONUT, NRI, and PNI indexes showed that 220 (14.73%), 703(47.60%), and 174 (11.65%) patients, respectively, had moderate to severe malnutrition. Patients with malnutrition determined by any of the three malnutrition indices were mainly older, had lower BMI, lower handgrip strength, and presented with more advanced tumor stage (**Supplementary Tables 2–4**). All malnutrition indices were correlated with each other (CONUT vs. PNI, $r = -0.657$, $P < 0.001$; CONUT vs. NRI scores, $r = -0.672$, $P < 0.001$; PNI vs. NRI scores, $r = 0.716$, $P < 0.001$, **Supplementary Figure 2**), but showed a weak concordance **(Supplementary Table 5).** In addition, all malnutrition indices were weakly correlated with PG-SGA ($r = 0.278$ for CONUT; $r = -0.173$ for PNI, and $r = -0.300$ for NRI, all $P < 0.001$) and had low validity (AUC = 0.595 for CONUT, AUC = 0.545 for PNI, and AUC = 0.617 for NRI) and reliability ($\kappa = 0.18$ for CONUT, $\kappa = 0.07$ for PNI, and $\kappa = 0.23$ for NRI) compared with the PG-SGA **(Supplementary Table 6).** Notably, 174 (11.65%) patients were classified as having malnutrition by all of the three malnutrition indices, and 409 (27.38%) patients were not diagnosed with malnutrition based on the three scores (**Figure 1A**). Analysis of BMI showed that participants with lower BMIs had a higher prevalence of malnutrition compared with those with higher BMI (**Figure 1B**). Most patients with a BMI above 25 kg/m^2 were also diagnosed with malnutrition by the three malnutrition indices: CONUT (159, 46.49%), NRI (169, 49.42%), and PNI (21, 6.14%).

Malnutrition Indices and Mortality

A total of 692 (46.32%) patients died within a median follow-up of 43.1 months. Univariable predictors of mortality for this study population are presented in **Supplementary Table 7**. Malnutrition status was correlated with a higher incidence of mortality regardless of the malnutrition index used. Incidence rates for the three indexes (events per 1,000 person-years) were as follows: CONUT (254.18), PNI (429.91), and NRI (261.87). Poor malnutrition status was correlated with poor OS,

TABLE 3 | Comparative analysis of the discrimination and model performance of each malnutrition index for all-cause mortality.

	CONUT		NRI		PNI	
C-index	0.607(0.585–0.630)		0.641(0.619–0.663)		0.557(0.534–0.581)	
	CONUT vs. NRI		CONUT vs. PNI		NRI vs. PNI	
	Difference	*P*-value	Difference	*P*-value e	Difference	*P*-value e
cNRI	−0.025	0.553	−0.081	0.058	−0.086	0.06
IDI	−0.01	0.368	0.029	0.11	−0.019	0.214
Model	C–index	*P*-value	cNRI	*P*-value	IDI	*P*-value
TNM stage	0.713(0.693–0.732)	Ref	Ref		Ref	
TNM stage +CONUT	0.731(0.712–0.750)	<0.001	0.139	0.016	0.025	<0.001
TNM stage +NRI	0.732(0.713–0.751)	<0.001	0.237	0.006	0.018	0.004
TNM stage +PNI	0.723(0.703–0.742)	<0.001	0.196	0.01	0.015	0.004

CONUT, Controlling Nutritional Status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

independent of whether the scores were analyzed as a continuous (**Figure 2A**) or a categorical variable (**Table 2**). Kaplan–Meier curves and adjusted curves were used to explore the relationship between malnutrition status and overall survival (**Figure 2B** and **Supplementary Figure 3**). Specific analysis by tumor location (lung, digestive, or other) is presented in **Supplementary Table 8**. After exclusion of 6 months mortality (209, 13.99%), a significant correlation between malnutrition status and OS was observed (**Supplementary Table 9**).

A comparison of the malnutrition index is summarized in **Table 3**. C-index analyses were performed to compare the clinical implications of the three malnutrition indices. NRI showed the highest C-index for OS (0.641, 95%CI 0.62–0.66), followed by CONUT (0.61, 95% CI0.59–0.63), and PNI (0.56, 0.53–0.58). In addition, NRI exhibited a significantly higher AUC value compared with the other two malnutrition indices (**Supplementary Figure 4**). However, NRI score performance was similar with CONUT and PNI indexes at predicting OS, as shown by the discrimination index values (**Supplementary Figure 5**). Findings on OS prediction showed that each of the three malnutrition indices had a significant prognostic value on the TNM classification system. NRI index showed the highest incremental value.

Relationship Between Malnutrition and Qol and Immunotherapy

The relationship between malnutrition status and symptom components of the Qol is presented in **Supplementary Tables 10–12**. Deterioration of nutritional status was independently associated with worsening of most of the symptoms (PF, RF, CF, SF, QL, FA, NV, PA, DY, SL, AP, FI, $P < 0.05$). The findings showed a deterioration in PF across malnutrition categories, despite having good PS (ECOG < 2). A similar pattern was observed with RF, CF, SF, QL, FA, and AP ($P < 0.05$ **Supplementary Tables 13–15**). Patients were stratified to explore the correlation between malnutrition status and immunotherapy outcomes. The findings showed that patients with a poor malnutrition status who underwent immunotherapy had a poor prognosis (**Supplementary Table 16** and **Supplementary Figure 6**).

DISCUSSION

The current study included elderly cancer patients. Out of the total patients included in the study, patients classified as malnourished ranged between 11.65 and 58.70% based on different screening tools. Moderate to severe malnutrition, dependent upon the tool used, ranged from 11.65 to 47.60%. Notably, malnutrition was prevalent even in overweight or obese patients. Most patients with a BMI > 24 were diagnosed with malnutrition (47.46% with CONUT, 7.03% with PNI, and 48.24% with NRI). Malnutrition was prevalent in elderly patients with cancer, and it is associated with all-cause mortality regardless of the malnutrition index used tumor types, and other risk factors. Moreover, malnutrition was associated with functional decline and was correlated with deterioration of Qol in elderly patients with cancer. In addition, changes in nutritional status were correlated with the prognosis of immunotherapy.

A previous study had reported that the nutritional assessment tool is associated with poor outcomes in elderly patients with cancer (3). Notably, only few studies have fully explored the prevalence and prognostic value of malnutrition index in elderly patients with cancer (18). The current study comprises a growing elderly population, and malnutrition is highly prevalent (19). Notably, aging and lack of physical activity are risk factors for malnutrition in the elderly (20). Malnutrition assessment should be carried out in inpatient facilities and should be recommended as a necessity to increase anticancer treatment efficacy. Although being underweight is a criterion of undernutrition, being overweight or obese does not protect against malnutrition (21). A previous study had shown that 20% of elderly cancer patients with malnutrition were obese. BMI was found to be a less valid screening tool for determining malnutrition in elderly patients with cancer (22).In addition, the use of individualized nutritional support is recommended in elderly patients with cancer who are already malnourished or are at a risk of becoming malnourished (23). These patients are predisposed to age-related sarcopenia and reduced gastrointestinal absorption (24).

With more sophisticated use of nutritional intervention, early identification of malnutrition is important, especially with the emphasis on patient-centered care (25). Severe malnutrition

scoring indexes, such as the CONUT, PNI, and NRI have been developed and validated in the past to help in the identification of inflammatory or malnourished patients at the risk of complications (26). Serum albumin can accurately reflect both nutritional and inflammatory status and is independently correlated with survival in patients with colorectal cancer (27). NRI is different from CONUT and PNI indexes as it includes both anthropometric factors and serum markers. In this study, NRI showed the highest incremental value in predicting mortality risk compared with CONUT and PNI indexes. However, these three indices were weakly correlated with PG-SGA and had low validity and reliability compared with the PG-SGA. One possible explanation is that PG-SGA predominantly relies on subjective answers of patients, but the nutritional index used in this study considers only objective variables. Subjective variables often entail patient participation, which may be time consuming and affected by patient perceptions (28). Particularly, concordance among scores for identifying degrees of malnutrition was rather poor, suggesting that they are not interchangeable (13).

Elderly patients with cancer exhibit several complications owing to their higher risk of malnutrition. Malnourished patients present with poor PS due to fatigue, loss of control and independency, high level of systemic inflammation, and ultimately impairing Qol (29, 30). Moreover, the traditional outcome of OS may be inappropriate in elderly patients (31). Previous studies report that poor nutritional status is correlated with poor Qol, for patients treated with curative and palliative interventions (32). A multicenter study comprising of 1,027 advanced cancer patients reported that malnutrition, PS (ECOG), and systemic inflammation were significantly correlated with poor Qol (33). The findings of the current study showed that malnutrition is correlated with poor Qol, even in patients with good PS. A high level of malnutrition was correlated with high levels of systemic inflammation. Meanwhile, several proinflammatory cytokines, such as TNF alpha, IL 6, and hormones would be produced by the tumor directly or systemically in response to the tumor, which had also been reported in the pathogenesis of malnutrition (21, 34). Malnutrition is a common cause of secondary immunologic dysfunction, as it results in a decrease in the total lymphocyte count (13, 35). Lymphocytes, mainly CD4+ and CD8+ T cells, play important roles in the immune response to immunotherapy (36). Consistent with this finding, the current study showed that patients with poor nutritional status had poor OS after receive immunotherapy.

The present study had several limitations. Data included in the study were limited to Chinese patients. Differences in genetic background, lifestyle, and diets may contribute to the differences in the Chinese population compared with other populations. Additionally, there are some potential selection bias, information bias, and residual confounding in our study in that we are not able to conduct a comprehensive geriatric assessment in elderly patients with cancer (37, 38). Some geriatric predictors such as depression, dementia, frailty, and functional impairment were not collected at the beginning of the study. Meanwhile, all of the patients in this study were inpatients and nutritional assessment was conducted only at admission. The study did not explore changes in nutritional status over time and their relationship with Qol and mortality. However, to the best of our knowledge, the current study is the first to explore the relationship between malnutrition index, Qol, and all-cause mortality in a large number of elderly patients with cancer. The study population was representative of the general Chinese elderly patients diagnosed with cancer.

In summary, malnutrition was prevalent in elderly cancer patients, regardless of the assessment tools used. Malnutrition was correlated with lower Qol and poor immunotherapy response. Moreover, malnutrition is a potential independent prognostic factor in elderly patients with cancer. Therefore, assessment of nutritional status may be important for the management of elderly patients with cancer. Optimizing Qol and prolonging the survival time is the central tenet of cancer care in elderly cancer 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 ethics committee of army medical center of PLA. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-PS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. H-PS and QZ conception and design. H-PS financial support. H-PS administrative support. X-RL, XZ, C-HS, RB, Y-ZG, J-SD, LQ, MT, C-LH, K-HW, H-XX, TL, and INSCOC group provision of study materials or patients. MT, XZ, and QZ collection and assembly of data: QZ, LQ, TL, J-SD, and Z-WW data analysis and interpretation. QZ manuscript writing. All authors contributed to the article and approved the submitted version.

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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.2021.738550/full#supplementary-material

Supplementary Table 1 | Procedures for the evaluation of each nutritional index.

Supplementary Table 2 | Baseline Characteristics of the Study Population stratified by CONUT.

Supplementary Table 3 | Baseline Characteristics of the Study Population stratified by NRI.

Supplementary Table 4 | Baseline Characteristics of the Study Population stratified by PNI.

Supplementary Table 5 | Kappa agreement for CONUT, PNI, NRI index.

Supplementary Table 6 | Sensitivity, specificity, positive predictive value and negative predictive value for CONUT, PNI, NRI index compared with PG-SGA.

Supplementary Table 7 | Univariable Cox regression analyses of factors predicting all-cause mortality.

Supplementary Table 8 | Multivariate Cox proportional hazards analyses of malnutrition indexes to predict all-cause mortality according to the location of cancer.

Supplementary Table 9 | Multivariate Cox proportional hazards analyses of malnutrition indexes to predict all-cause mortality according to exclude patients died within 6 months.

Supplementary Table 10 | Each parameter of EORTCQLQ–C30 stratified by CONUT.

Supplementary Table 11 | Each parameter of EORTCQLQ–C30 stratified by NRI.

Supplementary Table 12 | Each parameter of EORTCQLQ–C30 stratified by PNI.

Supplementary Table 13 | Each parameter of EORTCQLQ–C30 (with ECOG less than 2) stratified by CONUT.

Supplementary Table 14 | Each parameter of EORTCQLQ–C30 (with ECOG less than 2) stratified by NRI.

Supplementary Table 15 | Each parameter of EORTCQLQ–C30 (with ECOG less than 2) stratified by PNI.

Supplementary Table 16 | Hazard risk for all-cause mortality in elder patients treated with immunotherapy.

Supplementary Figure 1 | Flow chart.

Supplementary Figure 2 | Correlation analysis of clinical parameters.

Supplementary Figure 3 | Adjusted Kaplan-Meier curves for all-cause mortality by the category of each malnutrition index in elderly patients with cancer. CONUT, Controlling Nutritional Status score; PNI, prognostic nutritional index; NRI, nutritional risk index. The value was adjusted for age, gender, body mass index, hypertension, other comorbidities disease, smoking, alcohol, tumor location, tumor stage, chemotherapy, immunotherapy, surgery, parenteral nutrition intervention, enteral nutrition intervention, ECOG, PG-SGA, handgrip strength, EORTCQLQ-C30. For NRI, total cholesterol and lymphocyte count were adjusted additionally. For PNI, lymphocyte count was adjusted additionally.

Supplementary Figure 4 | Time-dependent area under the curve (AUC) by the three malnutrition indexes.

Supplementary Figure 5 | Plot to graphically display Integrated Discrimination Improvement (IDI), continuous Net Reclassification Improvement (NRI), and median improvement, for the additional value of malnutrition scores to TNM stage as assessed by the paired difference of risk scores.

Supplementary Figure 6 | Kaplan-Meier curves for all-cause mortality by the nutritional status in elderly patients with cancer treatment with immunotherapy.

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Comparisons and Impacts of the Basic Components of Sarcopenia Definition and Their Pairwise Combinations in Gastric Cancer: A Large-Scale Study in a Chinese Population

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Background and Aims: Sarcopenia is negatively associated with clinical outcomes. However, the definitions of sarcopenia are inconsistent across international consensuses. Thus, the purpose of this study is to compare the impact of the basic definition components of sarcopenia and their combinations in post-operative complications and overall survival, aiming to find the best sarcopenia definition to stratify the prognosis in an Asian population.

Methods: A total of 1,307 patients who underwent curative surgery for gastric cancer from July 2014 to May 2019 were prospectively included. The basic sarcopenia components were measured pre-operatively, including low skeletal muscle mass index (LSMI), low skeletal muscle radiodensity (LSMD), low handgrip strength (LHGS), and low gait speed (LGS). Among them, LSMI and LSMD were measured using a CT post-processing software, LHGS was measured using an electronic hand dynamometer, and LGS was represented by a 6-m walk speed.

Results: For the single basic component, the muscle function parameters (LHGS or LGS) but not the muscle composition parameters (LSMI or LSMD) showed associations with post-operative complications and mortality. For the combination of the basic combinations, all statistically significant combinations included at least one muscle function parameter. The combination of muscle composition (LSMI or LSMD) and muscle function (LHGS or LGS) had a significantly higher area under the curve in the prediction of post-operative complications compared with the combinations of two muscle function parameters (LSMI plus LSMD) or two muscle composition parameters (LHGS plus LGS).

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Conclusions: Compared with muscle composition parameters (LSMI and LSMD), muscle function parameters (LHGS and LGS) are better predictors of post-operative complications and overall survival, which should be considered as the principal determinant in the sarcopenia definition. The definition of sarcopenia consists of muscle function (LHGS or LGS) and muscle composition (LSMI or LSMD) separately, which is better than the combination of the two muscle function parameters (LHGS plus LGS) or two muscle composition parameters (LSMI plus LSMD).

Keywords: sarcopenia, muscle mass, muscle radiodensity, handgrip strength, gait speed

INTRODUCTION

Gastric cancer is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. It is often diagnosed at an advanced stage and has a low survival rate (1). Despite significant improvements in treatment in recent years, the prognosis of gastric cancer remains poor. Patients with gastric cancer often experience appetite loss, diminished food intake, and a loss of muscle mass (2, 3). Sarcopenia severely influences patients with gastric cancer and is shown to be associated with disability, reduced therapy intolerance, decreased response to cancer therapy, increased post-operative complications, poor quality of life, and a shorter duration of survival (4–7).

Sarcopenia originally referred to the loss of muscle mass but is now considered a muscle disease characterized by several features, including altered muscle composition and the decline of muscle function. However, there is an ongoing debate about the best approach to define sarcopenia due to the different combinations of basic definition components. The European Working Group on Sarcopenia in Older People (EWGSOP) put forward the first practical diagnostic criteria for sarcopenia in 2010 (8), in which sarcopenia was determined by low muscle mass accompanied by low muscle strength or low physical performance. Subsequently published guidelines have proposed similar definitions, with low muscle mass as the prerequisite (9–12).

Although a loss of muscle mass and a loss of muscle function were frequently correlated, the loss of muscle function was often more predominant than that of muscle mass (13). An increasing number of studies in recent years have shown that handgrip strength and gait speed are strong predictors of adverse clinical outcomes (14–16). Moreover, muscle quality, such as muscle radiodensity, is emerging as a new indicator for muscle composition and shows a significant association with poor clinical outcomes (17, 18). Thus, there have been heated arguments regarding the principal determinant in defining sarcopenia. In 2019, EWGSOP updated its original definition (EWGSOP2) (19), with low muscle strength replacing the role of muscle mass as the principal determinant. According to EWGSOP2, patients were considered to have probable sarcopenia when low muscle strength was detected, and the diagnosis was further confirmed by the presence of low muscle quantity or quality.

Inconsistent with EWGSOP2, the Asian Working Group for Sarcopenia 2019 (AWGS2019) retained its previous definition of sarcopenia (12) and adopted wider ranges of cut-off values for low handgrip strength and low physical performance in the updated 2019 consensus (20), which added more confusion to the clinical application of sarcopenia diagnosis due to the inconsistency between EWGSOP2 and AWGS2019. Up until now, the basic components of sarcopenia definition generally consist of two groups and four sub-groups across different consensuses, namely, muscle composition (low muscle quantity and low muscle quality) and muscle function (low muscle strength and low physical performance). However, to date, there have been no studies investigating the various impacts of different combinations of these components on post-operative outcomes and mortality in patients with gastric cancer.

The purpose of this study is to investigate the impacts of the low skeletal muscle mass index (LSMI), low skeletal muscle radiodensity (LSMD), low handgrip strength (LHGS), low gait speed (LGS), and their combinations on clinical outcomes, to determine the best sarcopenia definition to stratify the risk of post-operative complications and mortality in patients with gastric cancer.

MATERIALS AND METHODS

Patients

Patients who underwent surgical resection with curative intent for gastric cancer at the First Affiliated Hospital of Wenzhou Medical University were prospectively enrolled in this study. The inclusion criteria were: (1) at least 18 years of age; (2) had a histologically confirmed gastric adenocarcinoma; (3) planned to receive elective curative gastric surgery; (4) had abdominal CT scans within 1 month before surgery in our hospital. The exclusion criteria were as follows: (1) had a history of cancer; (2) had a local recurrence or distant metastasis of gastric cancer; (3) was unable to undergo functional assessments due to physical or mental causes; (4) data on muscle mass and muscle quality were unavailable due to unqualified CT images. Informed consent had been signed by all participants. All the patients signed informed consent after being informed that their clinical information will be used anonymously for research. This study was approved by the ethics committees of The First Affiliated Hospital of

Wenzhou Medical University and all procedures followed were in accordance with the Helsinki Declaration of 1964 and later versions.

Assessments of Muscle Quantity and Quality

One of the gold standard methods in detecting body composition and abnormal body composition phenotypes is a CT assessment (19, 21). Both CT-derived total abdominal muscle areas and mean skeletal muscle radiodensity (SMD) were used to represent muscle quantity and quality according to EWGSOP2 and AWGS2019. The cross-sectional CT image at the third lumbar vertebra (L3) level was selected and a Hounsfield unit (HU) threshold of −29 to +150 was used to distinguish the muscle from other nearby tissues (22). To minimize measurement bias, a trained investigator (FMZ) identified the muscle, and the areas and mean SD were calculated automatically using a CT post-processing software (GE ADW 4.5). The muscle areas were divided by the square of the height to obtain the skeletal muscle mass index (SMI) (cm^2/m^2). Low muscle mass as represented by the LSMI was defined as <40.8 cm^2/m^2 for males and <34.9 cm^2/m^2 for females (23). Low muscle quality as represented by LSMD was defined as <38.5 HU for males and <8.6 HU for females (24).

Assessments of Muscle Strength and Physical Performance

Handgrip strength and gait speed (GS) were used to represent muscle strength and physical performance. Handgrip strength (HGS) was measured on the dominant hand with an electronic hand dynamometer (EH101; Camry, Guangdong Province, China). The patients were seated comfortably with their shoulder adducted and neutrally rotated, their elbow flexed at 90°, and the forearm and wrist in a neutral position, and then asked to squeeze the dynamometer in their dominant hand with full force (25). According to the AWGS2019, LHGS (A-LHGS) was defined as <28 kg for males and <18 kg for females; according to the EWGSOP2, LHGS (E-LHGS) was defined as <27 kg for males and <16 kg for females.

Physical performance was assessed by the usual GS on a 6-m course (26). The patients started to walk at a normal speed under the command of an examiner. The time was recorded between the first footfall and the first foot crossing the 6-m end line. According to the AWGS2019, LGS (A-LGS) was defined as <1 m/s; according to the EWGSOP2, LGS (E-LGS) was defined as ≤0.8 m/s.

The HGS and GS were assessed by trained investigators (SLW and ZLS) once the patients were hospitalized, and the maximal value of the HGS and GS were recorded in three consecutive tests.

Diagnosis of Sarcopenia

According to the AWGS2019, sarcopenia was defined as low muscle mass plus low muscle strength and/or low physical performance (20). According to the EWGSOP2, sarcopenia was defined as low muscle strength plus low muscle quantity and/or low muscle quality (19).

Data Collection

Clinical data were collected prospectively and maintained in a digital database. For each patient, the data were collected by trained surgeons (FMZ, SLW, and ZLS), and discrepancies were solved by referring to an adjudicator (CLZ). The following data were collected: age, gender, BMI, smoking history, alcohol drinking history, reduced food intake (<50% of energy requirements >1 week, or any reduction for >2 weeks), weight loss (>5% within the past 6 months or >10% beyond 6 months), nutritional risk screening (NRS) 2002, Charlson comorbidity index (CCI) score, American Society of Anesthesiologists (ASA) score, hemoglobin concentration (anemia was defined as hemoglobin concentration <120 g/L for males and <110 g/L for females), albumin concentration (hypoalbuminemia was defined as albumin concentration <35 g/L), tumor-nodule-metastasis (TNM) stage, laparoscopic surgery, post-operative hospital stay, cost, and 30-day post-operative complications classified as Grade II or above according to the Claviene–Dindo classification (27).

Follow-Up

All the patients received regular telephone interviews or outpatient reviews after surgery. A follow-up was conducted every 3 months for the first 2 years after surgery and once every 6 months thereafter. The content of the follow-up included post-operative life, physical examination, image logical examinations, endoscopy, and laboratory tests. Overall survival (OS) was calculated from the time of surgery to the time of death or the last follow-up. The latest follow-up date was February 2020.

Statistical Analysis

The categorical data were represented as counts with percentages and compared using a Pearson's chi-square test or Fisher's exact test. The continuous data were represented as mean with an SD or median with an interquartile range (IQR) and compared using Student's *t*-test or Mann–Whitney *U*-test. Sarcopenia definition has four basic components, namely, LSMI, LSMD, LHGS, and LGS; however, a sarcopenia definition that consists of three and more (up to four) basic components is not practical as the incidence of sarcopenia by this definition would be very low, which is inconsistent with reality. Logistic regression analyses were used to investigate the association of the single component of sarcopenia definition (LSMI, LSMD, LHGS, and LGS) and their pairwise combinations (LSMI plus LSMD, LSMI plus LHGS, LSMI plus LGS, LSMD plus LHGS, LSMD plus LGS, and LHGS plus LGS) with 30-day post-operative complications. The Cox proportional hazard regression model was used to investigate the association of those components and their combinations with mortality. To avoid multicollinearity, the basic sarcopenia components and their combinations were included separately in the multifactor analysis model. The proportional hazards assumption was checked for all variables using Kaplan–Meier curves or Schoenfeld residual plots. To further reduce the interference of confounding factors and to verify the stability of the results, a total of three incremental models with increasing numbers of varieties were created to investigate the impact of the incremental adjustment. Model 1 was unadjusted. Model 2 was adjusted for age and gender. Model 3 was adjusted for

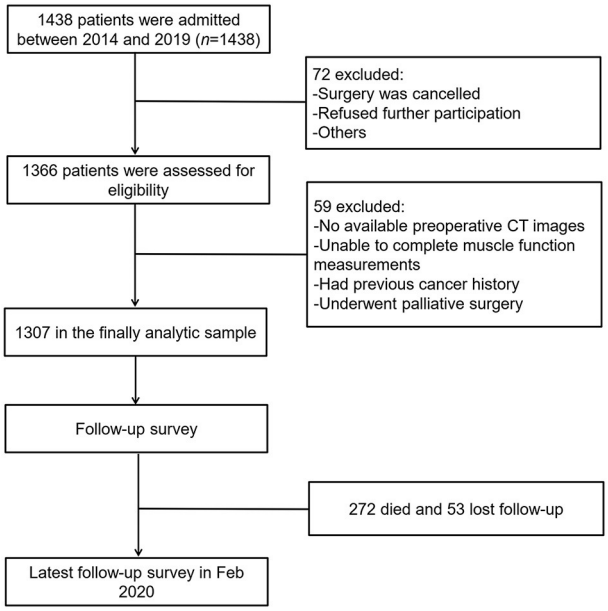

FIGURE 1 | Flowchart of patient selection.

Model 2 plus smoking history, alcohol drinking history, BMI, reduced food intake, weight loss, NRS 2002, CCI score, ASA score, anemia, hypoalbuminemia, TNM stage, and laparoscopic surgery. All analyses were performed with SPSS statistics version 23 (IBM, Armonk, NY, USA).

RESULTS

Characteristics of the Patients

From July 2014 to May 2019, a total of 1,366 patients were enrolled in our study. Fifty-nine patients who did not meet the inclusion criteria were excluded, and 1,307 cases were analyzed. The process of patient selection is shown in **Figure 1**, and the different combinations of basic sarcopenia definitions are shown in **Supplementary Figure 1**. Of the 1,307 patients who underwent sarcopenia assessments, there were 409 with LSMI, 579 with LSMD, 480 with A-LHGS, 625 with A-LGS, 402 with E-LHGS, and 254 with E-LGS. The different combinations of the basic components of sarcopenia definition resulted in different population sizes, ranging from 127 to 334 cases (**Supplementary Figure 1**). Finally, 298 and 287 cases were diagnosed as AWGS2019-sarcopenia and EWGSOP2-sarcopenia, respectively.

Baseline characteristics are shown in **Table 1**. The median age was 66 years, and 73.6% of patients were males. Compared with the total cohort, the patients with sarcopenia tended to be older, have lower BMI, SMI, SMD, HGS, and GS, and have increased hospital stay and cost. Compared with AWGS2019-sarcopenia, the patients with EWGSOP2-sarcopenia were older, more likely to be male, and had higher BMI and SMI but lower HGS. The other clinical characteristics were similar between AWGS2019 and EWGSOP2.

Impacts of the Basic Components of Sarcopenia Definition on the Post-operative Complication and Mortality

The odds ratio (OR) and hazard ratio (HR) of post-operative complications and mortality for the different basic components are shown in **Figure 2**, with the corresponding estimates presented in **Supplementary Table 1**. The incidence of post-operative complications was 21.7% (284/1,307) in the total cohort. In the final model, the muscle composition parameters including LSMI and LSMD were not associated with post-operative complications nor mortality. In contrast, A-LHGS (OR = 1.481, 95% CI = 1.092–2.007, $P = 0.011$) and E-LHGS (OR = 1.606, 95% CI = 1.177–2.191, $P = 0.003$) were significantly associated with post-operative complications. The E-LGS (HR = 1.582, 95% CI = 1.169–2.142, $P = 0.003$) was significantly associated with mortality.

Considering the significant and distinct impacts of E-LHGS and E-LGS on post-operative complications and mortality, we compared the SMI and SMD between E-LHGS and E-LGS (**Supplementary Table 2**). We found that the patients with E-LGS had significantly lower SMI (39 vs. 40.5 cm^2/m^2, $P = 0.014$) and SMD (32.5 vs. 35.0 HU, $P < 0.001$) compared with E-LHGS.

Impacts of Different Pairwise Combinations of Basic Components on the Post-operative Complication and Mortality

The OR and HR values with statistical significance are ranked in **Figure 3**, with the corresponding estimates presented in **Supplementary Table 3**. Whether for post-operative complications or mortality, all statistically significant combinations included at least one muscle function parameter, and the strongest combinations were those that consisted of both muscle function and muscle composition. For post-operative complications, the strongest combination was E-LHGS plus LSMI (OR = 1.659, 95% CI = 1.118–2.463, $P = 0.012$). For mortality, the strongest combination was E-LGS plus LSMD (HR = 1.6, 95% CI = 1.155–2.217, $P = 0.005$). The combination of LSMI plus LSMD was neither associated with post-operative complication nor mortality.

Given the important role of muscle function, we proposed an alternative sarcopenia definition, which was defined as the presence of E-LHGS or E-LGS plus LSMI or LSMD. For post-operative complications (**Table 2**), the EWGSOP2-sarcopenia (OR = 1.856, 95% CI = 1.324–2.602, $P < 0.001$) and the new-definition sarcopenia (OR = 1.655, 95% CI = 1.191–2.299, $P = 0.003$) showed statistical significance in the final model. However, none of the definitions were associated with mortality in the multivariate analysis (**Table 3**).

Additionally, to examine the impacts of these pairwise combinations on predicting post-operative complications and mortality, a receiver operating characteristic (ROC) curve was performed (**Figure 4**) with the corresponding estimates presented in **Supplementary Tables 4, 5**. The combination of muscle function (LSMI or LSMD) plus muscle composition

TABLE 1 | Patient baseline characteristics.

Factors	Total (n = 1,307)	AWGS2019[a]-sarcopenia (n = 298)	EWGSOP2[b]-sarcopenia (n = 287)	P-value[c]
Age, year	66.0 (14.0)	72.5 (11.3)	74 (10)	0.042*
Gender				0.003*
Male	962 (73.6)	203 (68.1)	227 (79.1)	
Female	345 (26.4)	95 (31.9)	60 (20.9)	
BMI, kg/m^2	22.5 (4.0)	20.6 (3.5)	21.5 (4.0)	<0.001*
SMI, cm^2/m^2	42.4 (10.3)	34.7 (6.8)	38.5 (8.9)	<0.001*
SMD, HU	37.2 (10.1)	33.3 (9.4)	32.1 (8.6)	0.080
HGS, mean (SD), kg	27.7 (9.0)	21.8 (7.4)	19.1 (5.8)	<0.001*
GS, m/s	1.0 (0.3)	0.86 (0.23)	0.85 (0.29)	0.801
Smoking				0.402
Yes	328 (25.1)	65 (21.8)	71 (24.7)	
No	979 (74.9)	233 (78.2)	216 (75.3)	
Alcohol drinking				0.519
Yes	256 (19.6)	49 (16.4)	53 (18.5)	
No	1,051 (80.4)	249 (83.6)	234 (81.5)	
Reduced food intake				0.251
Yes	403 (30.8)	126 (42.3)	108 (37.6)	
No	904 (69.2)	172 (57.7)	179 (62.4)	
Weight loss				0.709
Yes	297 (22.7)	83 (27.9)	76 (26.5)	
No	1.010 (77.3)	215 (72.1)	211 (73.5)	
NRS 2002 ≥ 3				0.159
Yes	465 (35.6)	172 (57.7)	149 (51.9)	
No	842 (64.4)	126 (42.3)	138 (48.1)	
CCI score				0.472
0	960 (73.5)	212 (71.1)	191 (66.6)	
1	243 (18.5)	54 (18.1)	62 (21.6)	
≥2	104 (8.0)	32 (10.8)	34 (11.8)	
ASA score ≥ 3				0.933
Yes	154 (11.8)	47 (15.8)	46 (16.0)	
No	1,153 (88.2)	251 (84.2)	241 (84.0)	
Anemia				0.690
Yes	457 (35.0)	155 (52.0)	154 (53.7)	
No	850 (65.0)	143 (48.0)	133 (46.3)	
Hypoalbuminemia				0.141
Yes	305 (23.3)	114 (38.3)	127 (44.3)	
No	1,002 (76.7)	184 (61.7)	160 (55.7)	
TNM stage				0.731
I	491 (37.5)	87 (29.2)	76 (26.5)	
II	316 (24.2)	79 (26.5)	82 (28.6)	
III	500 (38.3)	132 (44.3)	129 (44.9)	
Laparoscopic surgery				0.384
Yes	470 (36.0)	95 (31.9)	82 (28.6)	
No	837 (64.0)	203 (68.1)	205 (71.4)	
Post-operative hospital stay, day	13.0 (7.0)	14.0 (9.0)	15.0 (8.0)	0.115
Cost, Yuan	59,893 (22,610)	67,266 (27,418)	68,488 (27,035)	0.248

Numbers are median (interquartile range) or number (%), unless otherwise stated.

**Statistically significant ($P < 0.05$).*

[a]*Includes patients who had low SMI (LSMI) plus low HGS (LHGS) or those who had LSMI plus low GS (LGS).*

[b]*Includes patients who had LHGS plus LSMI or those who had LHGS plus low SMD (LSMD).*

[c]*Comparison between AWGS2019-sarcopenia and EWGSOP2-sarcopenia.*

AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; SD, standard deviation; BMI, body mass index; SMI, skeletal muscle mass index; SMD, skeletal muscle radiodensity; HU, Hounsfield unit; HGS, handgrip strength; GS, gait speed; NRS, nutritional risk screening; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; TNM, tumor-nodule-metastasis.

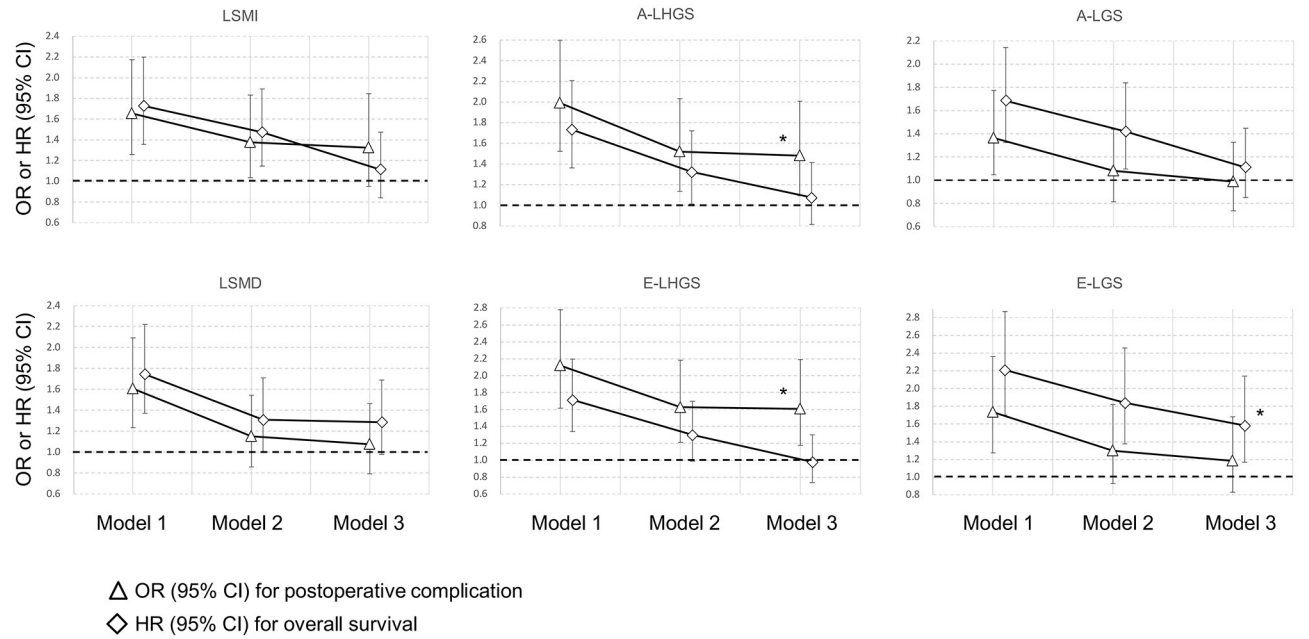

FIGURE 2 | Association of basic sarcopenia components with clinical outcomes. *Statistically significant. A, Asian Working Group for Sarcopenia; E, European Working Group on Sarcopenia in Older People; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; LHGS, low handgrip strength; LGS, low gait speed.

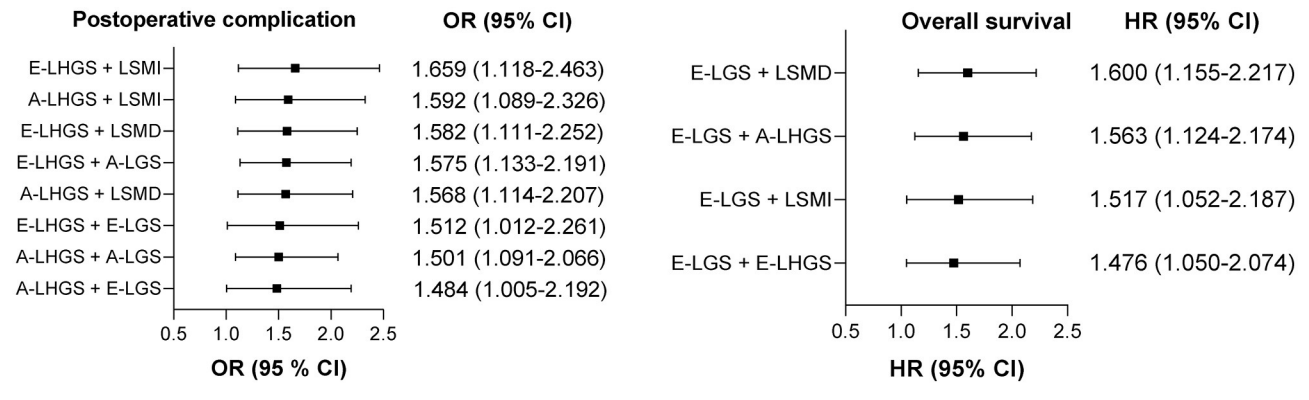

FIGURE 3 | Ranking of the relationship strength of the associations between different pairwise combinations of basic components and clinical outcomes. A, Asian Working Group for Sarcopenia; E, European Working Group on Sarcopenia in Older People; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; LHGS, low handgrip strength; LGS, low gait speed.

(LHGS or LGS) had a significantly higher area under the curve [0.598, 95% CI = 0.57–0.626)] in the prediction of post-operative complications compared with the combinations of the two muscle function parameters (LSMI plus LSMD) [0.546, 95% CI = 0.517–0.575)] or two muscle composition parameters (LHGS plus LGS) [0.553, 95% CI = 0.524–0.581)]. These three types of combinations had no statistical difference in predicting mortality, but the combination of muscle composition plus muscle function showed a trend of a higher area under the ROC curve (AUC) in a longer follow-up period.

DISCUSSION

In the current study, we demonstrated that the muscle function measured as LHGS and LGS was a better predictor of post-operative complications and mortality than the muscle composition measured as LSMI and LSMD. Additionally, we found that LHGS is a strong predictor of post-operative complications, while LGS is a strong predictor of mortality. Moreover, the sarcopenia definition consisting of both muscle function parameters (LHGS or LGS) and muscle composition parameters (LSMI or LSMD) had stronger impacts on the

TABLE 2 | Impact of different sarcopenia definitions on post-operative complications.

Factors	OR (95% CI)	*P*-value
LSMI plus (LHGS[a] or LGS[a]) [AWGS2019 definition]		
Model 1	1.900 (1.420–2.544)	<0.001*
Model 2	1.459 (1.066–1.997)	0.018*
Model 3	1.416 (0.996–2.012)	0.053
LHGS[b] plus (LSMI or LSMD) [EWGSOP2 definition]		
Model 1	2.595 (1.942–3.467)	<0.001*
Model 2	1.947 (1.413–2.683)	<0.001*
Model 3	1.856 (1.324–2.602)	<0.001*
(LHGS[b] or LGS[b]) plus (LSMI or LSMD)		
Model 1	2.387 (1.811–3.147)	<0.001*
Model 2	1.779 (1.300–2.435)	<0.001*
Model 3	1.655 (1.191–2.299)	0.003*

**Statistically significant (P < 0.05).*
[a]Defined by AWGS2019.
[b]Defined by EWGSOP2.
Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was adjusted for Model 2 plus BMI, smoking history, alcohol drinking history, reduced food intake, weight loss, NRS 2002 ≥3, CCI score, ASA score ≥3, anemia, hypoalbuminemia, TNM stage, and laparoscopic surgery.
AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; LHGS, low handgrip strength; LGS, low gait speed; OR, odds ratio; CI, confidential interval.

TABLE 3 | Impact of different sarcopenia definitions on overall survival.

Factors	HR (95% CI)	*P*-value
LSMI plus (LHGS[a] or LGS[a]) [AWGS2019 definition]		
Model 1	2.040 (1.584–2.626)	< 0.001*
Model 2	1.629 (1.239–2.142)	< 0.001*
Model 3	1.236 (0.915–1.671)	0.167
LHGS[b] plus (LSMI or LSMD) [EWGSOP2 definition]		
Model 1	2.084 (1.612–2.695)	< 0.001*
Model 2	1.544 (1.159–2.058)	0.003*
Model 3	1.076 (0.795–1.458)	0.635
(LHGS[b] or LGS[b]) plus (LSMI or LSMD)		
Model 1	1.953 (1.528–2.496)	< 0.001*
Model 2	1.440 (1.085–1.911)	0.011*
Model 3	1.122 (0.835–1.508)	0.446

**Statistically significant (P < 0.05).*
[a]Defined by AWGS2019.
[b]Defined by EWGSOP2.
Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was adjusted for Model 2 plus BMI, smoking history, alcohol drinking history, reduced food intake, weight loss, NRS 2002 ≥3, CCI score, ASA score ≥3, anemia, hypoalbuminemia, TNM stage, and laparoscopic surgery.
AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; LHGS, low handgrip strength; LGS, low gait speed; HR, hazard ratio; CI, confidential interval.

clinical outcomes when compared to the combinations of two muscle function parameters (LHGS plus LGS) or two muscle composition parameters (LSMI plus LSMD). These findings suggest that muscle function should be considered as the principal determinant in the diagnosis of sarcopenia, and muscle composition is also necessary for the diagnosis.

Previous studies have examined the association of muscle function and muscle composition with clinical outcomes. Sato et al. showed that pre-operative LHGS but not low lean body mass was significantly associated with grade 2 or higher morbidities in patients who underwent curative surgery for gastric cancer (28). A large, multiethnic, national study showed that LGS defined by <0.8m/s had a stronger association with death in the elderly compared with low lean mass (29). In our study, we obtained similar results, in which muscle function was found to be a better indicator as compared with muscle composition to predict post-operative complications and mortality. Notably, LHGS and LGS had different impacts on clinical outcomes; LHGS was strongly associated with post-operative complications, while LGS was strongly associated with mortality.

With respect to the different impacts of LHGS and LGS on clinical outcomes, Revenig et al. found that LHGS but not LGS showed a significant association with short-term morbidity and mortality in patients who underwent major abdominal operations (30). On the other hand, the HUNT II study reported no association of the different tertiles of HGS with mortality (31). An observational study conducted on more than 500,000 participants found that slow walking speed but not weak handgrip strength was associated with an increased risk of mortality in the low-BMI subset (15). A recent study also reported that it was LGS but not LHGS that showed significant association with mortality (32).

Although the exact reason for the different impacts of LHGS and LGS is unclear, this phenomenon may be partly explained in two ways. First, HGS as a form of explosive isometric force is significantly associated with the capacity of substrate reservation and utilization (33), systemic inflammation (34), and abnormal metabolism (35). Patients with LHGS are more likely to have increased complications due to their poor adaptability to surgical strikes. Second, LGS accounts for the 70% increase in the disability of cancer patients (32). The loss of mobility is likely to lead to the vicious cycle of decreased physical activity and contributes directly to a higher risk of mortality (26). Our analysis revealed that patients with LGS had worse muscle conditions than those with LHGS, which justified the hypothesis that the patients with LGS had worse survival due to their poor physical fitness. In the EWGSOP2, gait speed only serves as a severity indicator of sarcopenia diagnosis. In our study, LGS defined by the EWGSOP2 (<0.8 m/s), but not AWGS2019 (<1 m/s), and was found to be an independent risk factor for mortality. Our study indicated that LGS alone and its combination with muscle composition (LSMI or LSMD) were strong predictors of adverse clinical outcomes, which should also be considered as the prerequisite of sarcopenia definition like LHGS.

Few studies explored different combinations of the basic components of sarcopenia definition. Rodrigues et al. found that LSMI plus LSMD had the strongest association with 1-year mortality compared with LSMI alone or LSMD alone (36). However, their study did not adjust the nutrition-related

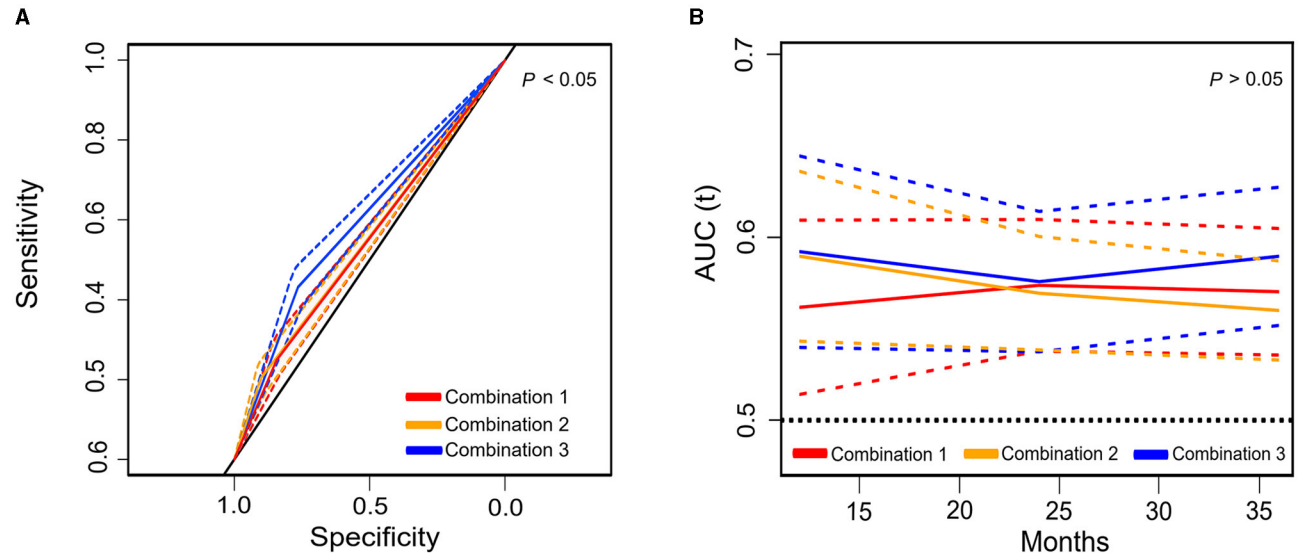

FIGURE 4 | The area under the receiver operating characteristic (ROC) curve (solid line) and 95% CI (dotted line) of different pairwise combinations of basic components for post-operative complications **(A)** and mortality **(B)**. Combination 1: LSMD plus LSMI; Combination 2: E-LHGS plus E-LGS; Combination 3: (E-LHGS or E-LGS) plus (LSMD or LSMI); E, European Working Group on Sarcopenia in Older People; ROC, receiver operating characteristic curve; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; LHGS, low handgrip strength; LGS, low gait speed; CI, confidential interval.

variables in the analysis model, such as reduced food intake, weight loss, NRS 2002, anemia, and hypoalbuminemia. In our study, LSMI plus LSMD showed a higher risk of mortality than LSMI alone or LSMD alone in the unadjusted model, and the model adjusted for sex and age. However, the association attenuated to insignificance in the final model, which included more nutritional parameters.

Although LSMI or LSMD alone were not related to clinical outcomes, we found that their combinations with LHGS and LGS improved the predictive effect of LHGS alone or LGS alone in post-operative complications and mortality. In concordance with our study, Gan et al. found that the risk of non-alcoholic fatty liver disease increased when low muscle mass and LHGS were simultaneously detected compared with only one of them detected (37). Furthermore, Maurício et al. demonstrated that low muscle mass in combination with low muscle strength instead of other nutritional parameters had the strongest association with complications in patients with colorectal cancer (38).

However, the existing evidence is scattered. There is a paucity of previous studies to systematically compare the impacts of different combinations of the basic components of sarcopenia definition on clinical outcomes in one cohort. No study has yet discussed the impacts of LSMD plus LHGS, LSMD plus LGS, and LHGS plus LGS on clinical outcomes. Our findings extended the previous evidence by reporting that muscle function should be considered as the principal determinant in the diagnosis of sarcopenia. Sarcopenia defined by both muscle function and muscle composition had a stronger impact on the clinical outcomes when compared with that of muscle function alone or muscle composition alone. Our results indicated that the combination of muscle function plus muscle composition had the best ability to predict post-operative complications and a trend of higher mortality prediction ability in a longer follow-up period when compared with the combination of muscle composition plus muscle composition or muscle function plus muscle function.

Our results are supported by interventional research. With the development of perioperative management, pre-operative functional intervention gained increasing attention in the team-based approach and the enhanced recovery after surgery pathway. Pre-habilitation combining endurance and resistance training has been shown to improve physical capacity and muscle strength and decrease post-operative complications (39–41). Patients who do more exercise were observed to have a lower risk of mortality and recurrence (42). The associations of LHGS and LGS with clinical outcomes reported in our study emphasize the importance of pre-habilitation and rehabilitation in patients with gastric cancer.

The present study has some potential limitations. First, the observational design of our study does not allow us to draw firm conclusions on the causal role of muscle function and muscle composition in post-operative complications or mortality. However, data were prospectively collected to minimize the recall bias and many potential confounding factors were adjusted, including BMI, reduced food intake, and weight loss, which are strong predictors of clinical outcomes in patients who underwent abdominal operations (43). Second, the cut-off values for LSMI and LSMD were obtained from our previous large-scale studies (23, 24) due to the lack of a unified standard on the cut-off values for CT-assessed LSMI and LSMD. The existing cut-off values were mainly derived from populations that were not Chinese (44, 45). We believe that using cut-off values from Chinese-specific large sample studies can yield more accurate results under the

consideration of the race differences between Chinese and other populations. Third, the analysis of this study was conducted in patients with gastric cancer, which may limit the generalization of the conclusion. Fourth, we were unable to calculate the sensitivity and specificity of our definitions in the present study because sarcopenia currently lacks a gold standard.

In conclusion, this study found that muscle function has stronger impacts on clinical outcomes compared with muscle composition. Low handgrip strength is a strong predictor of post-operative complications, and LGS is a strong predictor of mortality. The sarcopenia definition that consists of both muscle function and muscle composition showed the strongest impacts on clinical outcomes. These findings suggested that the definition of sarcopenia should be constructed using muscle function as the principal determinant and that this should be used together with muscle composition.

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 for Clinical Research of the First Affiliated Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-LZ and ZY designed the study. ZZ provided technical support. F-MZ, S-LW, and Z-LS collected the data. X-ZZ, ZY, X-LC, and XS did the analysis and interpretation of data. F-MZ and H-PS wrote the article. X-ZZ and ZY revised the article and took the decision to submit the article for publication. All authors contributed to the article and approved the submitted version.

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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.2021.709211/full#supplementary-material

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Association Between the Nutritional Risk and the Survival Rate in Newly Diagnosed GIST Patients

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Background: Currently, the incidence of gastrointestinal stromal tumors (GIST) is increasing rapidly worldwide. Malnutrition may increase the risk of perioperative complications and affect the prognosis of patients. However, previous studies on the nutritional status of GIST patients and its impact on prognosis are limited. Therefore, this study aims to explore the incidence of malnutrition in newly diagnosed GIST patients, the proportion of participants in need of nutritional intervention, and the relationship between nutritional status and overall survival (OS).

Methods: We retrospectively analyzed the clinical data of GIST patients treated in our hospital from January 2014 to January 2018. Nutritional Risk Screening 2002 (NRS2002) and Patient-Generated Subjective Global Assessment (PG-SGA) were used to assess the nutritional status of all patients. This study was to investigate the clinical significance of PG-SGA by analyzing the relationship between PG-SGA score and OS.

Results: A total of 1,268 newly diagnosed GIST patients were included in this study, of which 77.76% were at risk of malnutrition (NRS2002 score $\geq$ 3), and the incidence of malnutrition was 10.09% (PG-SGA score $\geq$ 4). Meanwhile, we found 2.29% of the patients required urgent nutritional support (PG-SGA score $\geq$ 9). Multivariate analysis showed that age ($p = 0.013$), BMI ($p = 0.001$), weight loss ($p = 0.001$), anemia ($p = 0.005$), pre-albumin ($p = 0.010$), albumin ($p = 0.002$), tumor location ($p = 0.001$), tumor size ($p = 0.002$), and NIH classification ($p = 0.001$) were risk factors for nutritional status. The prognosis was significantly in GIST patients with different PG-SGA score at admission ($p < 0.05$).

Conclusion: This study suggested that malnutrition is common in newly diagnosed GIST patients, and the higher the PG-SGA score, the worse the clinical outcome.

Keywords: nutrition status, PG-SGA, NRS2002, gastrointestinal stromal tumors (GIST), risk factor, prognosis

INTRODUCTION

Gastrointestinal stromal tumors (GIST) is the most common mesenchymal tumor in the gastrointestinal tract, which is often caused by the mutation of KIT and PDGFRA genes (1, 2). The incidence of GIST is increasing at an alarming rate worldwide (3). Numerous studies have demonstrated that nutritional deficiency account for about 85% of all patients diagnosed with cancer, of whom about 50–90% have weight loss and malnutrition at the beginning of treatment (4–6). Malnutrition in patients with malignant tumors can lead to low immune function, increase perioperative infection rates, prolong hospitalization time, increase medical costs, and more importantly, affect quality of life and prognosis (7–9). In addition, the relative risk of cancer deaths caused by malnutrition is 1.8 times that of patients without malnutrition (10, 11). Therefore, it is of great importance to assess the nutritional status of patients during cancer treatment to comprehensively evaluate their tolerance to treatment.

The incidence of malnutrition in gastrointestinal tumors, especially upper gastrointestinal tumors, is higher than that in non-gastrointestinal tumors (12, 13). However, most studies investigating the gastrointestinal tumors focus on the nutritional status of non-GIST cancers, such as gastric cancer and colon cancer, while few people pay attention to the nutritional status of GIST patients, and there is no consensus on nutritional guidelines for GIST patients. As the symptoms of GIST are usually non-specific, most patients are in advanced stage at the time of diagnosis. The oppression or obstruction caused by the tumor leads to malabsorption. This results in higher risk of malnutrition, especially in patients undergoing perioperative treatment and patients with advanced and recurrent metastasis (14, 15). Therefore, correction of the malnutrition in GIST patients is particularly important for improving the quality of life and significantly prolonging the survival period.

Currently, the nutritional assessment for patients with malignant tumors generally adopts anthropometric measurements, serum biochemical indicators, Nutritional Risk Screening 2002 (NRS2002), and Patient-Generated Subjective Global Assessment (PG-SGA). According to the expert consensus of the European Society of Parenteral and Enteral Nutrition (ESPEN), once patients are diagnosed with malignant tumors, NRS2002 is the first choice for screening and assessment of nutritional status, and PG-SGA is the preferred tool for assessment (16, 17). In addition, PG-SGA was also accepted as a nutritional assessment standard for cancer patients by the Oncology Nutritional Dietetic Practice Group of the American Diet Association (18).

However, there is no standard nutritional assessment method for newly diagnosed GIST patients. And there is no conclusion the preferred choice of assessment tool for nutritional status in GIST patients. Moreover, studies on the nutritional assessment of GIST patients are scarce, with only very few studies on the application of NRS2002 combined with PG-SGA in the evaluation of newly diagnosed GIST patients. Therefore, the purpose of this study is to use the NRS2002 combined with PS-SGA score to evaluate the nutritional status of newly diagnosed GIST patients and analyze the impact of their nutritional status on prognosis.

METHODS AND MATERIALS

Patient Section

This study retrospectively analyzed the medical data of 1,268 patients with newly diagnosed GIST admitted to the Fourth Hospital of Hebei Medical University from January 2014 to January 2018. Inclusion criteria were as follows: (1) pathological diagnosis was GIST; (2) without preoperative antitumor treatment; and (3) complete follow-up and clinical data. Exclusion criteria were as follows: (1) the patient had accepted antitumor therapies before surgery; (2) patients with cognitive impairment or other acute psychological problems; (3) without complete medical records and laboratory results; (4) the patient lost post-operative follow-up. This study was tested and approved by the ethics committee of The Fourth Hospital of Hebei Medical University, and the patients provided informed consent.

Assessment Method

All patients were screened by NRS2002 score after admission. The score $\geq$3 indicates a risk of malnutrition in patients, which needs further assessment by PG-SGA. PG-SGA score includes patient self-assessment and medical staff assessment, which includes seven areas. Patients' self-assessment includes weight changes, dietary intake, self-reported symptoms, activities and function, and medical staff assessment includes nutrition-related disease status, metabolic status, physical examination. Each of these seven areas is given a score of 0–4, and the sum of scores obtained in each area is divided into quantitative and qualitative evaluations, thus providing guidance on the level of nutrition and drug intervention required by each patient. Quantitative evaluation is defined as follows: PG-SGA score of 0–1 indicates that nutritional support not required and treatment in the future based on routine re-evaluation, 2–3 points indicate malnutrition or suspected malnutrition, 4–8 points indicate moderate malnutrition, and $\geq$9 points indicate severe malnutrition. Qualitative evaluation indicates that patients with score of 4–8 need nutritional intervention and symptomatic treatment, and patients with score $\geq$9 need urgent symptomatic treatment and appropriate nutritional support before anti-tumor treatment.

Clinicopathological Parameters and Definitions

We collected the basic data of newly diagnosed GIST patients including gender, age, weight, etc. Laboratory tests include routine blood tests and biochemical tests. Preoperative examination included abdominal computed tomography (CT), nuclear magnetic resonance imaging (MRI) and gastrointestinal endoscopy. Pathology and gene detection included tumor location, tumor size, mitotic count, immunohistochemistry, risk classification, c-kit exons 9, 11, 13 and 17, and PDGFRA exons 12 and 18. The risk classification standard we adopted is the 2008

version of the improved National Institutes of Health (NIH) classification (19).

Follow-Up

All patients were recommended to have a follow-up visit every 3 months in the first 2 years, and every 6 months after 2 years. All patients were followed up as outpatients. The latest follow-up date was in December 2020, and the median follow-up time was 68.6 months (range 16–76 months). The total survival time was calculated from diagnosis to death or the last follow-up. Overall survival (OS) was defined as time interval from operation to tumor-related death or last contact, and OS was the preferred destination.

Statistical Analyses

We provided PG-SGA standard questionnaires for all newly diagnosed GIST patients admitted to the Third Department of the Fourth Hospital of Hebei Medical University. Software of SPSS version 21.0 and GraphPad Prism 5.01 were utilized to perform statistical analyses. Anthropometric measurement and PG-SGA scores were expressed in the form of descriptive statistics (mean, standard deviation, and frequency), respectively. The *t* test, ANOVA test, and correlation analysis were used to statistically evaluate the degree of correlation between these factors and the PG-SGA score. Survival analysis was performed using the Kaplan-Meier method. Univariate and multivariate analyses were investigated by the Cox proportional hazards regression model. The hazard ratio (HR) and 95% confidence interval (CI) were used to assess relative risks. P value < 0.05 was regarded as statistical difference significantly.

RESULTS

Clinicopathological Features of Newly Diagnosed GIST Patients

A total of 1,268 patients were admitted from January 2014 to January 2018, including 887 cases (69.95%) of tumors located in the stomach, 54 cases (4.26%) in the duodenum, 235 cases (18.53%) in the intestine, 30 cases (2.37%) in the colon, and 62 cases (4.89%) in the mesentery. All GIST patients were confirmed by pathology. There were 665 males (52.44%) and 603 females (47.56%), with a median age of 59 (19–76) years old. The median diameter of the tumor was 6 (2.3–15.4) cm, and the median nuclear mitotic figure was 5 (3–13) / 50HPF (**Table 1**).

TABLE 1 | General and tumor characteristics of study participants ($n = 1268$).

Variables	*N* (Percentage)
Age (years)	59.9 ± 4.2 *
Sex (male)	665 (52.44%)
Weight loss	
No WL (0–1.9% of body weight)	801 (63.17%)
Mild WL (2–2.9% in 1-month or 2–5.9% in 6 months)	208 (16.40%)
Moderate WL (3–4.9% in 1-month or 6–9.9% in 6 months)	117 (9.23%)
Severe WL (5–9.9% in 1-month or10–19.9% in 6 months)	88 (6.94%)
Very severe WL (>10% in 1-month or >20% in 6 months)	54 (4.26%)
Tumor location	
Stomach	887 (69.95%)
Duodenum	54 (4.26%)
Intestine	235 (18.53%)
Colon	30 (2.37%)
Mesentery	62 (4.89%)
Tumor size (cm)	
<5.0	383 (30.21%)
5.0~10.0	789 (62.22%)
>10.0	96 (7.57%)
Nuclear mitotic figure (50HPF)	
<5	372 (29.34%)
6~10	708 (55.84%)
>10	188 (14.83%)
NIH classification	
High risk	279 (22.00%)
Moderate risk	543 (42.82%)
Low risk	309 (24.37%)
Very low risk	137 (10.80%)
Ki-67 percentage	
≤10%	848 (66.88%)
>10%	420 (33.12%)
c-kit exons	
Positive	961 (75.79%)
Negative	307 (24.21%)
PDGFRA exons	
Positive	319 (25.16%)
Negative	949 (74.84%)

**Mean ± SD.*

Nutritional Status of Newly Diagnosed GIST Patients

Figure 1 presents the nutritional risk and assessment of 1,268 newly diagnosed GIST patients. A total of 1,268 newly diagnosed GIST patients were screened by NRS2002, and 986 patients (77.76%) had the risk of malnutrition (NRS2002 score ≥ 3), while 282 patients (22.24%) did not have the risk of malnutrition (NRS2002 score < 3). The PG-SGA evaluation of 1,268 patients showed that 64.11% of the patients scored 0–1 points, indicating a good nutritional status, and nutritional support was not needed. 23.50% of the patients scored 2–3 points, so only nutritional guidance was needed. And 10.09% of the patients scored 4–8 points, indicating that there was mild/moderate malnutrition, and nutritional intervention and treatment were needed. 2.29% patients scored >9 points, indicating severe malnutrition and urgent need for symptomatic treatment and adequate nutritional support. This study also found that only 117 (74.52%) of the 157 patients who needed nutritional intervention (PG-SGA score ≥ 4) received nutritional support one week before the treatment. 2.37% of patients received parenteral nutrition (PN) support, 12.07% received enteral nutrition (EN) support, and 2.13% received both EN and PN support. In addition, we also found that 93 patients (7.33%) with good nutrition (PG-SGA score < 4) received nutritional support treatment (**Table 2**).

According to 2008 version NIH stromal tumor risk classification standard, 1,268 patients were divided into

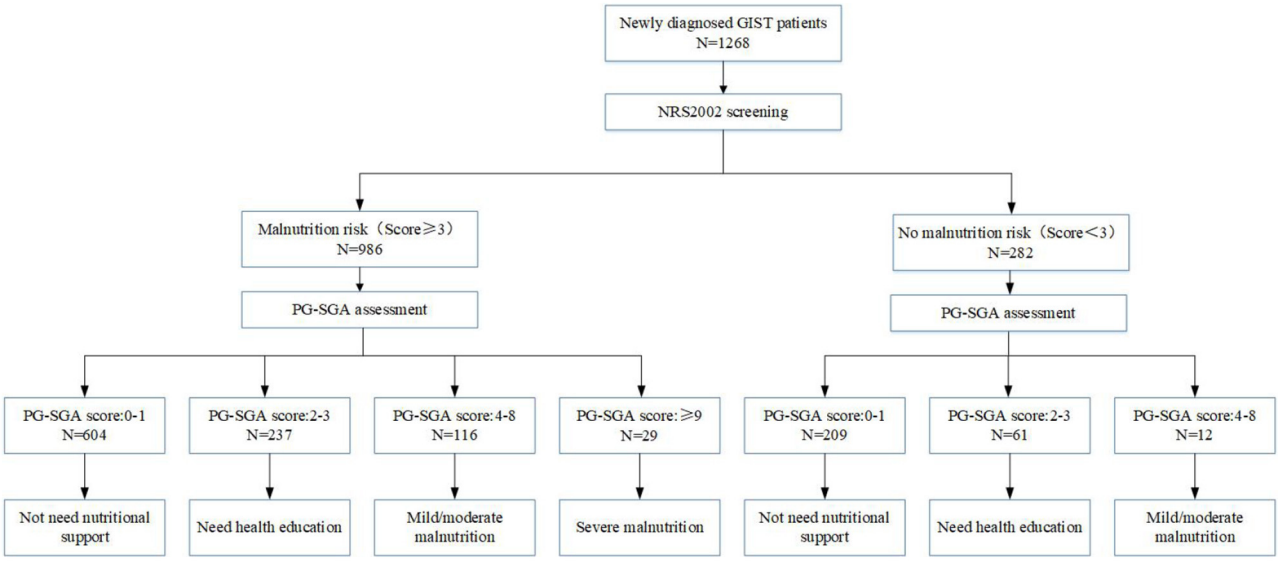

FIGURE 1 | Nutrition screening and assessment of 1,268 newly diagnosed GIST patients.

TABLE 2 | Patient-generated subjective global assessment classification and nutritional therapy situation ($N = 1,268$).

Nutrition support	Total (%)	PG-SGA			
		0∼1(%)	2∼3(%)	4∼8(%)	≧9(%)
No	1058 (83.43)	779 (95.82)	239 (80.20)	38 (29.69)	2 (6.90)
Yes					
PN	30 (2.37)	0 (0)	5 (1.68)	14 (10.94)	11 (37.93)
EN	153 (12.07)	34 (4.18)	52 (17.45)	57 (44.53)	10 (34.48)
EN and PN	27 (2.13)	0 (0)	2 (0.67)	19 (14.84)	6 (20.69)

PN, parenteral nutrition; EN, enteral nutrition; PG-SGA, patient-generated subjective global assessment.

TABLE 3 | The relationship between risk classification and incidence of nutritional risk in newly diagnosed GIST patients ($N = 1,268$) [n(%)].

Group	*N*	PG-SGA				Malnutrition incidence
		0∼1(%)	2∼3(%)	4∼8(%)	≥9(%)	
High risk	279	91 (32.62)	99 (35.48)	65 (12.54)	24 (8.60)	188 (67.38)
Moderate risk	543	323 (59.48)	159 (29.28)	56 (10.31)	5 (0.92)	220 (40.52)*
Low risk	309	269 (87.06)	33 (10.68)	7 (2.27)	0 (0)	40 (12.94)*
Very low risk	137	130 (94.89)	7 (5.11)	0 (0)	0 (0)	7 (5.11)*

**Compared with high risk group, two-sided chi-square test, all $p < 0.05$.*

TABLE 4 | Location of gastrointestinal stromal tumors and incidence of nutritional risk ($N = 1,268$) [n(%)].

Group	*N*	PG-SGA				Malnutrition incidence
		0∼1(%)	2∼3(%)	4∼8(%)	≥9(%)	
Stomach	887	605 (68.21)	180 (20.29)	88 (9.92)	14 (1.58)	282 (46.61)*
Duodenum	54	29 (53.70)	19 (35.19)	5 (9.26)	1 (1.85)	25 (46.30)*
Intestine	235	139 (59.15)	73 (31.06)	17 (7.23)	6 (2.55)	96 (40.85)*
Colon	30	20 (66.67)	6 (20.00)	3 (10.00)	1 (3.33)	10 (33.33)*
Mesentery	62	20 (32.26)	20 (32.26)	15 (24.19)	7 (11.29)	42 (67.74)

**Compared with mesentery group, two-sided chi-square test, all $p < 0.05$.*

four groups. There were 137 patients in the extremely low risk group, 7 (5.11%) of whom were at risk of malnutrition. There were 309 cases in the low-risk group, of which 40 (12.94%) patients had the risk of malnutrition. There were 543 patients in the moderate-risk group, 220 (40.52%) of whom were at risk of malnutrition. There were 279 cases in the high-risk group, of which 188 (67.38%) patients had the risk of malnutrition. The comparison between groups showed that the risk of malnutrition in the high-risk group was significantly higher than that in the other three groups ($p < 0.05$) (**Table 3**).

A total of 1,268 patients were divided into five groups according to the location of tumor. Among the 887 cases of gastric stromal tumors, 282 cases (46.61%) had malnutrition risk, while 96 of the 235 patients with intestinal stromal tumors were at risk of malnutrition (40.85%). There were 54 patients with duodenal tumors and 30 patients with colonic tumors, with 25 cases (46.30%) and 10 cases (33.33%) at risk of malnutrition, respectively. Meanwhile, there were 62 cases of stromal tumors in mesentery, and 42 cases (67.74%) had malnutrition risk. The comparison among groups showed that the risk of malnutrition in patients with mesentery stromal tumors was significantly higher ($p < 0.05$) (**Table 4**).

Analysis of Related Factors Affecting PG-SGA Score

Our study revealed the relationship between PG-SGA of newly diagnosed GIST patients scores and possible related factors. The PG-SGA related factors were patients' age ($p = 0.013$), BMI ($p = 0.001$), weight loss ($p = 0.001$), anemia ($p = 0.005$), pre-albumin ($p = 0.010$), albumin ($p = 0.002$), tumor location ($p = 0.001$), tumor size ($p = 0.002$), and NIH classification ($p = 0.001$) (**Table 5**).

Treatment and Prognosis of Newly Diagnosed GIST Patients

Among 1,268 newly diagnosed GIST patients, 1,046 patients (82.49%) underwent direct surgical resection, and 222 patients (17.50%) received imatinib targeted therapy due to large tumor size. All patients were followed up for a median of 68.6 months (range 16–86). The 5-year OS rate was 74.61%, and the median survival time was 42.7 months (range 13–74). The 5-year OS rate of patients with NRS2002 score < 3 was 79.79%, while that of patients with NRS2002 score ≥ 3 was only 73.12%($p = 0.007$, **Figure 2A**). According to different PG-SGA scores, the stratified analysis of 1,268 patients with PG-SGA evaluation showed that the 5-year OS of patients with PG-SGA score of 0–1 and 2–3 was 78.60 and 73.93%, respectively, which was significantly better than that of patients with PG-SGA score > 3 ($p < 0.001$, **Figure 2B**). The prognosis of GIST patients with different PG-SGA scores in nutritional therapy and without any intervention was shown in **Figure 3**. For patients with PG-SGA score < 4, there was no significant difference in prognosis between nutritional therapy and non-nutritional intervention ($p = 0.164, 0.251$). However, for patients with PG-SGA score of $4 \sim 8$, especially those with PG-SGA score ≥ 9, nutritional therapy significantly improved the prognosis of patients, and the survival time was better than that of patients without nutritional intervention ($p = 0.025, 0.001$).

TABLE 5 | Analysis of PG-SGA score with factors affecting nutritional status.

Characteristic	Cases (n)	PG-SGA score (Median ± SD)	Statistical value	*P*-value
Age (years)			$u = -4.041$	0.013
≥60	718	5 ± 1.66		
<60	550	3 ± 1.32		
Sex			$t = 1.549$	0.083
Male	665	4 ± 1.47		
Female	603	3 ± 1.31		
BMI (kg/m^2)			u=11.421	0.001
<18.5	155	6 ± 2.19		
18.5∼25.0	878	4 ± 1.11		
>25.0	235	3 ± 0.86		
Weight loss			$u = 14.671$	0.001
No WL (<2% of body weight)	801	3 ± 0.87		
Mild WL (2–3% in 1-month or 2–6% in 6 months)	208	4 ± 1.89		
Moderate WL (3–5% in 1-month or 6–10% in 6 months)	117	5 ± 1.36		
Severe WL (5–10% in 1-month or10–20% in 6 months)	88	6 ± 2.07		
Very severe WL (>10% in 1-month or >20% in 6 months)	54	8 ± 1.25		
Anemia			$t = 9.997$	0.005
Yes	494	5 ± 1.76		
No	774	4 ± 0.88		
Pre-albumin (mg/dL)			$t = 23.043$	0.010
<20	390	6 ± 1.34		
≥20	878	4 ± 1.11		
Albumin(g/L)			$t = 11.034$	0.002
<35	338	5 ± 1.76		
≥35	930	3±0.97		
Tumor location			$u = 10.876$	0.001
stomach	887	3 ± 1.71		
duodenum	54	4 ± 1.38		
intestine	235	5 ± 1.65		
colon	30	5 ± 1.13		
mesentery	62	7 ± 1.44		
Tumor size (cm)			$u = 13.573$	0.002
<5.0	383	2 ± 1.02		
5.0∼10.0	789	4 ± 0.96		
>10.0	96	7 ± 2.15		
NIH classification			$u = 15.621$	0.001
High risk	279	7 ± 2.08		
Middle risk	543	5 ± 1.17		
Low risk	309	3 ± 0.88		
Very low risk	137	3 ± 1.22		

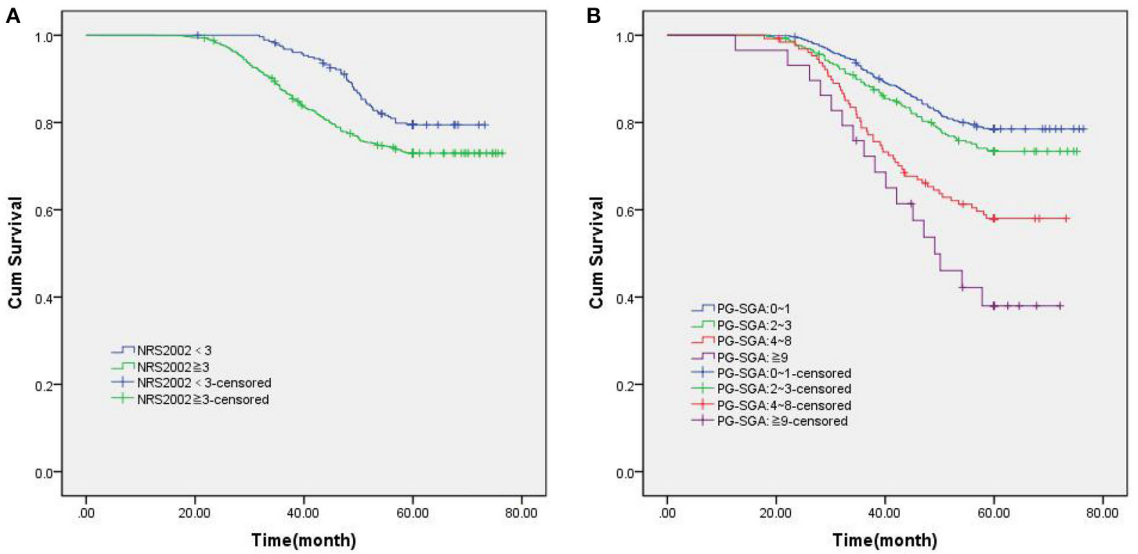

FIGURE 2 | Kaplan-Meier survival curves in patients with newly diagnosed GIST patients. **(A)** Overall survival based on NRS2002 scores; **(B)** Overall survival based on PG-SGA scores.

Univariate and multivariate analysis showed that PG-SGA score ($p = 0.001$, HR = 1.638, 95%CI: 1.259–2.441), pre-albumin ($p = 0.033$, HR = 0.687, 95%CI: 0.548–0.861), BMI($p = 0.011$, HR = 1.321, 95%CI: 0.925–1.874), NIH classification ($p = 0.000$, HR = 2.805, 95%CI: 2.241–3.510), nutritional therapy($p = 0.012$, HR = 1.267, 95%CI: 0.987–1.762) were independent risk factors affecting the 5-year OS rate of newly diagnosed GIST patients (**Table 6**).

DISCUSSION

GIST is the most common mesenchymal tumor in the gastrointestinal tract, accounting for about 2% of gastrointestinal tumors, which can occur throughout the gastrointestinal tract, also can occur in the mesangium, pelvis and retroperitoneum (20, 21). Due to the lack of specific manifestations of GIST, clinical symptoms such as gastrointestinal bleeding, abdominal pain and discomfort or abdominal mass often occur (22). The best time for early treatment has been delayed after symptom deterioration, and the 5-year survival rate has been greatly affected. Meanwhile, cancer patients are often accompanied by malnutrition in the initial diagnosis, especially digestive tract malignant tumors (23).

Our retrospective study was the first to investigate the nutritional status of newly diagnosed GIST patients and possible factors leading to malnutrition by NRS2002 combined with PG-SGA score. We found that 12.38% of newly diagnosed GIST patients were malnourished, and 2.29% of them needed urgent management to relieve malnutritional symptom and/or nutritional support. This is similar to the results of previous study conducted by Guo et al. (24) that the incidence of malnutrition was 12%, and the risk of malnutrition was 34%. Our results also discovered that malnutrition was common in newly diagnosed GIST patients, and these patients would need prompt nutrition and dietician education and guidance. This may be due to recurrent gastrointestinal symptoms such as anorexia and anorexia in GIST patients, which further leads to weight loss. In addition, the rapid growth of tumors, abdominal recurrence and systemic metastasis increased nutrition consumption, resulting in malnutrition in patients. Moreover, we found that the risk of malnutrition in patients in the high-risk group and in patients with tumors located in the mesentery was significantly higher than that in other groups.

We further analyzed the factors affecting PG-SGA score and found that tumor location and tumor risk classification were independent risk factors. Furthermore, we found that the PG-SGA score was closely related to the OS of patients. The 5-year OS rates of patients with 0–1 score were better than those of other groups, especially those with ≥4 scores. The higher PG-SGA score was associated with worse prognosis. These findings have also been supported by other studies. Ge et al. found that the nutritional status of patients with gastrointestinal cancer determines the quality of life during subsequent treatment (18). In addition, Tan et al. found that nutritional status assessed by PG-SGA may be a predictor of prognosis in patients with advanced cancer, especially in patients with gastrointestinal tumors (25). In view of these results, we speculate that PG-SGA score may exert a more effective value in evaluating the prognosis of newly diagnosed GIST patients.

There are still some limitations in our research. First, this study was a single-center retrospective study with limited number of cases. Second, only OS was investigated due to the lack of data on progression-free survival and quality of life. Therefore, further multicenter, prospective studies to more comprehensively assess the prediction values of NRS2002 combined with PG-SGA score on risk of adverse clinical outcomes in patients with GIST are still needed.

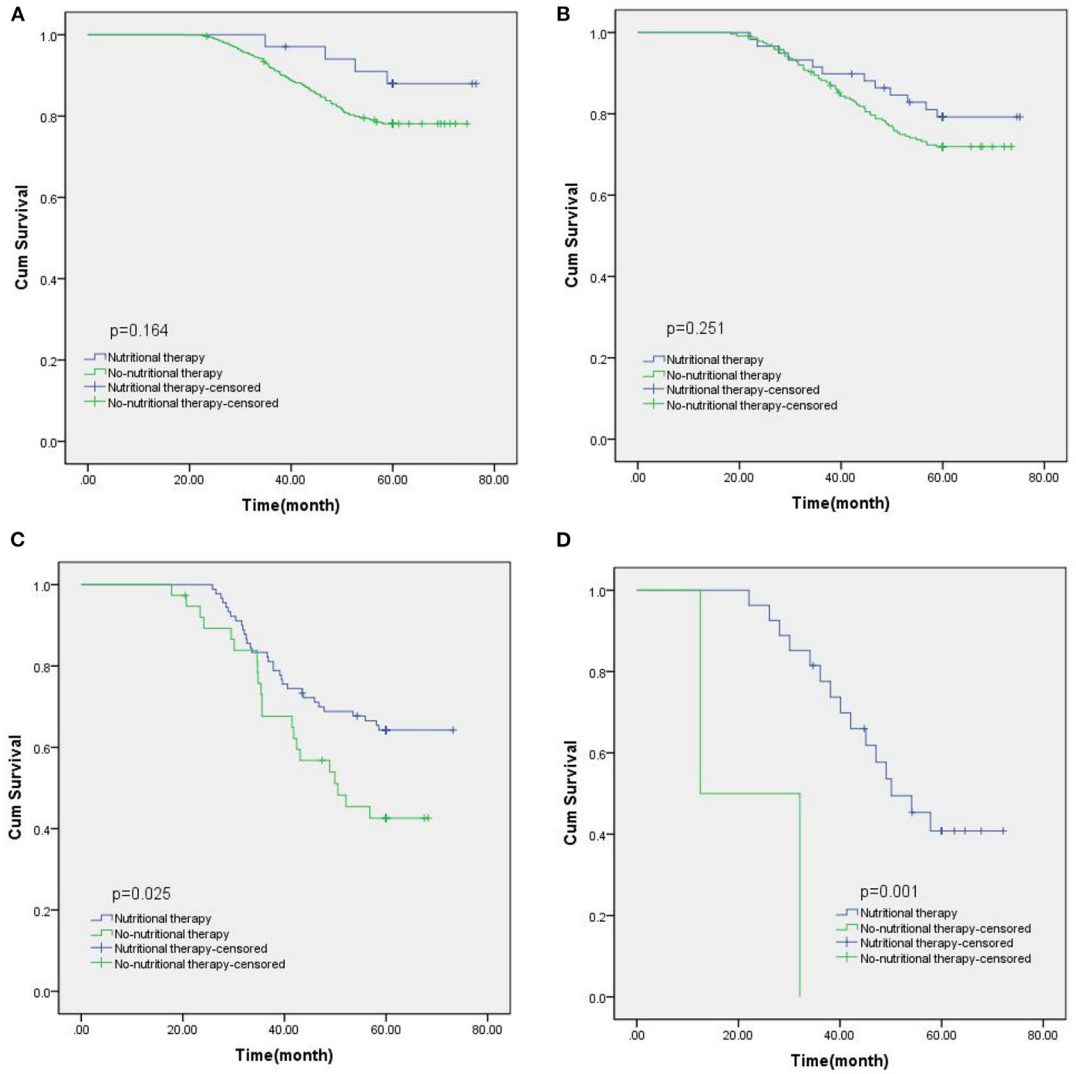

FIGURE 3 | The prognosis of GIST patients with different PG-SGA scores in nutritional therapy and without any intervention. **(A)** PG-SGA scores: 0∼1; **(B)** PG-SGA scores: 2∼3; (**C)** PG-SGA scores: 4∼8; **(D)** PG-SGA scores: ≥9.

TABLE 6 | Univariate and multivariate analyses for OS in patients with newly diagnosed GIST.

Variables	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Gender (female vs. male)	0.010	1.321	0.898–1.624	0.079	0.758	0.556–1.003
Age (≤60 vs. >60)	0.065	1.457	1.123–2.083	-	-	-
NRS2002(<3 vs. ≥3)	0.033	1.593	1.256–2.763	0.066	0.895	0.431–1.346
PG-SGA (0–1 vs. 2–3 vs. 4–8 vs. ≥9)	0.008	1.832	1.360–3.321	0.001	1.638	1.259–2.441
Anemia (Yes vs. no)	0.077	0.653	0.489–1.032	-	-	-
Pre-albumin (mg/dL) (<20 vs. ≥20)	0.048	1.032	0.783–1.439	0.033	0.687	0.548–0.861
Albumin (g/L) (<35 vs. ≥35)	0.031	1.329	1.102–1.876	0.054	0.772	0.542–1.302
BMI(<18.5 vs. ≥18.5 and <25.0 vs. ≥25.0)	0.022	1.487	1.212–2.034	0.011	1.321	0.925–1.874
NIH classification (High risk vs. moderate risk vs. low risk vs. very low risk)	0.001	3.458	2.198–5.329	0.000	2.805	2.241–3.510
Nutritional therapy (No vs. yes)	0.032	1.432	1.031–1.987	0.012	1.267	0.987–1.762

CONCLUSION

In this study, NRS2002 combined with PG-SGA score was used to evaluate the nutritional status of newly diagnosed GIST patients in China for the first time to the best of our knowledge. About 12.38% of GIST patients had malnutrition at the time of diagnosis, and more than 1/10 of GIST patients needed urgent nutritional intervention and management. More attention should be paid to the nutritional status of GIST patients, especially those with high risk of malnutrition, such as elderly patients and tumors located in the mesenteric. These high-risk patients should be timely PG-SGA assessment, and give nutritional education and necessary nutritional support.

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 tested and approved by the Ethics Committee of The Fourth Hospital of Hebei Medical University, and the patients provided informed consent. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QZ: conception and design, and administrative support. PD, PY, YT, HG, and YLi: provision of study materials or patients. PD, PY, YT, and HG: collection and assembly of data. PD and CS: data analysis and interpretation. PD, HG, PY, CS, YT, YLiu, YLi, and QZ: manuscript writing. All authors contributed to the article and approved the submitted version.

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Nutritional Risk, Health Outcomes, and Hospital Costs Among Chinese Immobile Older Inpatients: A National Study

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Purpose: Evidence of the impact of nutritional risk on health outcomes and hospital costs among Chinese older inpatients is limited. Relatively few studies have investigated the association between clinical and cost outcomes and nutritional risk in immobile older inpatients, particularly those with neoplasms, injury, digestive, cardiac, and respiratory conditions.

Methods: This China-wide prospective observational cohort study comprised 5,386 immobile older inpatients hospitalized at 25 hospitals. All patients were screened for nutritional risk using the Nutrition Risk Screening (NRS 2002). A descriptive analysis of baseline variables was followed by multivariate analysis (Cox proportional hazards models and generalized linear model) to compare the health and economic outcomes, namely, mortality, length of hospital stay (LoS), and hospital costs associated with a positive NRS 2002 result.

Results: The prevalence of a positive NRS 2002 result was 65.3% (n = 3,517). The prevalence of "at-risk" patients (NRS 2002 scores of 3+) was highest in patients with cardiac conditions (31.5%) and lowest in patients with diseases of the respiratory system (6.9%). Controlling for sex, age, education, type of insurance, smoking status, the main diagnosed disease, and Charlson comorbidity index (CCI), the multivariate analysis showed that the NRS 2002 score = 3 [hazard ratio (HR): 1.376, 95% CI: 1.031–1.836] were associated with approximately a 1.5-fold higher likelihood of death. NRS 2002 scores = 4 (HR: 1.982, 95% CI: 1.491–2.633) and NRS scores ≥ 5 (HR: 1.982, 95% CI: 1.498–2.622) were associated with a 2-fold higher likelihood of death, compared with NRS 2002 scores < 3. An NRS 2002 score of 3 (percentage change: 16.4, 95% CI: 9.6–23.6),

score of 4 (32.4, 95% CI: 24–41.4), and scores of ≥ 5 (36.8, 95% CI 28.3–45.8) were associated with a significantly (16.4, 32.4, and 36.8%, respectively) higher likelihood of increased LoS compared with an NRS 2002 scores < 3. The NRS 2002 score = 3 group (17.8, 95% CI: 8.6–27.7) was associated with a 17.8%, the NRS 2002 score = 4 group (31.1, 95% CI: 19.8–43.5) a 31.1%, and the NRS 2002 score ≥ 5 group (44.3, 95% CI: 32.3–57.4) a 44.3%, higher likelihood of increased hospital costs compared with a NRS 2002 scores < 3 group. Specifically, the most notable mortality-specific comorbidity and LoS-specific comorbidity was injury, while the most notable cost-specific comorbidity was diseases of the digestive system.

Conclusions: This study demonstrated the high burden of undernutrition at the time of hospital admission on the health and hospital cost outcomes for older immobile inpatients. These findings underscore the need for nutritional risk screening in all Chinese hospitalized patients, and improved diagnosis, treatment, and nutritional support to improve immobile patient outcomes and to reduce healthcare costs.

Keywords: nutrition risk, mortality, costs, length of stay, immobility, older inpatients

INTRODUCTION

Many older adults suffer from undernutrition that signals a generally poor nutritional status (1–6). The negative health impact of undernutrition is consistent across all age groups, and undernutrition tends to deteriorate during hospitalization, which worsens patient health outcomes, namely, increased frailty, institutionalization, heightened comorbidity, loss of independence, reduced quality of life, higher mortality, and increased hospital costs (4–9). Undernutrition in older adults owing to the lack of intake or uptake of nutrition leads to altered body cell mass and body composition, diminished physical and mental function, and impaired clinical outcomes from the disease (10, 11). We also know that age-related pathophysiological, psychosocial, and pharmacological factors determine changes in dietary habits, and the intake and use of nutrients, leading to specific nutritional deficits (12).

The worldwide prevalence of undernutrition among older hospital patients ranges from 30 to 50% of all admissions (10, 13–16), mainly due to deficiencies in the early assessment, identification, and adequate management of "at-risk" undernutrition patients. The need for comprehensive nutritional screening programs has been widely acknowledged (15), with the European Society for Parenteral and Enteral Nutrition (ESPEN) (17) recommending the Nutrition Risk Screening (NRS 2002) should be used to screen for undernutrition for all hospitalized patients. Several nutritional assessment tools, namely, the NRS 2002 and Short-Form Mini Nutritional Assessment, have been proposed as instruments to identify nutritional risk among hospitalized patients in China (14, 18). Unfortunately, nutritional risk screening is not performed in many Chinese hospitals, with mandatory nutritional risk screening only conducted in some, but not all, large-scale national, provincial, and municipal 500+ bed tertiary hospitals (19).

With the largest population in the world, China has a numerically large number of adults aged 65 years and older, with the ratio of non-working old age to working-age adults growing (20). The undernutrition risk, or high prevalence of undernutrition, in the growing older age population, points to a formidable healthcare burden (20, 21). Immobility is the main cause of deficient nutrient consumption among the elderly, where immobility decreases the ability of myofibrillar proteins to respond to amino acids, so-called anabolic resistance, which contributes to the decline in skeletal muscle mass (22). Older patients may also develop sarcopenia, where the loss of skeletal muscle mass and function is accelerated by immobilization, which frequently is manifested in the form of poor nutritional status (23, 24).

In China, there is a lack of studies addressing the impact of nutritional risk on health outcomes and health costs, especially in older inpatients with immobility. Our national prospective observational cohort study assesses the association between nutritional risk and clinical outcomes and hospital costs among hospitalized immobile older inpatients, and whether the associations differed by sex, age group (60–69, 70+), disease diagnosis, and Charlson comorbidity index (CCI) score.

METHODS

Study Design and Sample

Supported by the agenda of the National Health and Family Planning Commission to improve the outcomes among older inpatients, the target population is all older adults hospitalized in 25 general hospitals in China. To ensure the representativeness of the study sample, between November 2015 and July 2017, we used a two-stage stratified random sampling design to create a nationally representative sample of patients in China. In the first stage, a simple random sampling procedure was used to select five

Abbreviations: NRS 2002, The Nutritional Risk Screening 2002; BMI, body mass index; CCI, Charlson comorbidity index.

provinces and Beijing municipality in eastern China (Guangdong province, Zhejiang province, and Beijing municipal city), western China (Sichuan province), and central China (Henan province and Hubei province), a total of six tertiary hospitals enrolled in this stage. In the second stage, 11 secondary hospitals and eight community hospitals were randomly selected from the hospitals attached to these tertiary hospitals.

We collected data on immobile inpatients aged ≥ 65 years old; with basic physiological needs carried out in bed, except for active or passive bedside sitting/standing/wheelchair use for examination; and willingness to provide informed consent. A total of 5,386 participants were enrolled in the study, with follow-ups continuing 90 days after enrolment unless they died in the hospital or relinquished medical treatment.

Bioethics

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (S-700), and all participants, or their proxies, provided written informed consent before enrolment in the study. Records and information of patients were anonymized and de-identified before the analysis.

Data Collection

The data were collected by trained and certified registered nurses. To ensure data quality, the research group developed the project survey manual and operation manual. To ensure accurate data collection, all the nurses received systematic training and testing before they recorded information of patients and applied the NRS 2002. They are all proficient in the process of investigation. All questionnaire results were reviewed by the attentive head nurse in each ward to ensure the completeness and correctness of the raw data. Also, the research group established a quality control team, a communication platform based on the WeChat App to guarantee timely feedback. Proxy respondents, usually a spouse or other legal guardian, were interviewed when the patients were incapable of responding to the questions themselves.

Measurement of Nutritional Risk

According to the European Society for Parenteral and Enteral Nutrition (ESPEN) recommendations (17), Nutrition Risk Screening (NRS 2002) should be used to screen undernutrition in all hospitalized patients. Previous studies also indicated that the NRS 2002 has a high sensitivity (62%) and specificity (93%) and that the NRS score predicts clinical outcomes (18). Even when alternative measures, such as the Short-Form Mini Nutritional Assessment may be more suit for the assessment of the older adult (25, 26), large-scale national, and provincial tertiary hospitals in particular (19) were required to use the NRS 2002 for nutritional risk screening (18). Therefore, this study applied the NRS 2002 among the study participants.

Using NRS 2002, nutritional risk status and disease severity of patients were collected by nursing staff on admission (17). The "nutritional score" was defined by the adequacy of dietary intake due to three different parameters: (i) quartile decrease of estimated oral food intake requirements; (ii) presence of at least 5% weight loss within the previous 1–3 months; (iii) low body mass index (<18.5 kg/m^2). The NRS 2002 score was calculated by adding the "nutritional score" of 0–3 to the "disease severity score" of 0–3, plus one extra point for "older" patients, who were aged 70 years and older as a subset of all over 65-year-old participants. A total NRS 2002 score ≥ 3 was considered as nutritionally "at-risk," and the "disease severity score" was categorized as moderate = 3, high = 4, and very high = 5+ (8). NRS 2002 has a good prognostic value for a range of health outcomes, including mortality, with excellent test characteristics (8, 15), and has been validated for the Chinese population (18, 27).

Outcome Measures

The following outcomes were measured: death (all-cause mortality was recorded at 90 days, including in-hospital deaths, which were verified from death certificates), duration of hospitalization measured by the length of hospital stay (LoS), and hospital treatment costs. Treatment costs were derived from the Hospital Information System (HIS) in each hospital after the enrolled patients died or were discharged from the hospital. The HIS belongs to the financial system of the hospital, which records all the expenses incurred by the patient during their hospital stay.

Covariates

We collected sociodemographic variables and health-related variables, with the covariates selected based on previous research (8, 14–16, 28). The demographic characteristics included sex, age, education (illiteracy, primary school, junior high school, and high school and above), type of insurance [no insurance; New Cooperative Medical System (29); Urban Resident Basic Medical Insurance (30); and Urban Employee Basic Medical Insurance (31)], smoking status (never, current, and past smokers, which refers to at least 6 months without smoking), and disease diagnosis according to the International Classification of Diseases (ICD)-10 codes (circulatory system, neoplasms, injury, digestive system, respiratory system, and "other"). The CCI provides a reproducible tool to identify patients with multiple chronic diseases in a universally applicable, transparent, and auditable method. CCI measures multiple comorbidities by creating a sum score, weighted according to the presence of 19 comorbid conditions (32, 33). The CCI score was derived from the discharge ICD-10 codes and patient histories obtained from the HIS standardized case report forms. The total CCI score for each patient was categorized into four levels of comorbidity, 0 (none), 1 (moderate), 2 (severe), and 3+ (very severe) (33, 34).

Statistical Analyses

Statistical analysis was conducted using Stata version 14 for Windows (Stata Corp, College Station, TX, USA). Descriptive results are expressed as mean and SD or as number and percentage. Bivariate analyses were performed using the χ^2 test or Fisher's exact test for qualitative variables and Kruskal–Wallis test for quantitative variables. Cox proportional hazards models were constructed to determine the association of nutritional risk with mortality and a generalized linear model with a gamma distribution and a log link was used to assess the association

of LoS and hospital costs with the NRS 2002 score. The NRS 2002 score was modeled as both a continuous variable and a categorical variable (NRS 2002 < 3, 3, 4, 5+). The results were reported as hazard ratios (HRs) in mortality and reported as percentage changes (=exp∧coefficient-1) and 95% CIs in LoS and hospital costs. We adjusted for covariate factors in three stages: (1) we adjusted for age and sex; (2) we added education, insurance, and smoking status; and (3) we additionally adjusted for disease diagnosis and CCI score (the fully adjusted model). To examine the shape of the association between NRS 2002 scores and mortality, LoS, and hospital costs, we conducted a restricted cubic spline analysis. We analyzed whether the association of mortality, LoS, and hospital costs with the NRS 2002 score differed by sex, age group (60–69, 70+), disease diagnosis, and CCI score by separately adding an interaction term to the fully adjusted model. A P value of < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

As shown in the baseline sample characteristics in **Table 1**, 57.5% of patients (3,096/5,386) were men; half (49.9%) were aged 70 years and older; only 18.9% of patients were illiterate; most (80.5%) had insurance; and 70.5% were non-smokers (70.5%). The most frequent diseases were circulatory system diseases (31.5%), others (21.9%), and neoplasms (21.0%), with the proportion of patients with no comorbidities was 27.1%; one comorbidity 26.9%; two comorbidities 23.2%; and three or more comorbidities 22.8%.

NRS 2002 Scores

To assess nutritional status, NRS 2002 scores were calculated (**Table 1**). Of the patients studied, 34.7% (1,869/5,386) showed no risk (NRS 2002 < 3) after the initial screening, but 65.3% (3,517/5,386) were categorized as at risk of undernutrition. Among the patients at risk of undernutrition, **Table 1** shows that 24.51% (1,320/5,386) were at moderate risk (NRS 2002 = 3); 18.66% (1,005/5,386) were at high risk (NRS 2002 = 4); and 22.13% (1,192/5,386) were at very high risk (NRS 2002 ≥ 5) and were classified as undernourished. In **Table 1**, the highest prevalence of undernutrition was found in patients with the disease of the circulatory system.

Impact on Mortality, LoS, and Hospital Costs

Death occurred in 8.4% of patients (**Table 1**), the number of patients who died with no nutritional risk (NRS < 3) was 89 (4.8%); moderate nutritional risk (NRS 2002 = 3) was 105 (8.0%); high nutritional risk (NRS 2002 = 4) was 116 (11.5%); and very high nutritional risk (NRS 2002 ≥ 5) was 143 (12.0%) ($P < 0.001$). **Table 2** displays the association of nutritional risk with mortality, LoS, and hospital costs. The Cox proportional hazards model in **Table 2** indicates that after adjusting for potential covariates, NRS 2002 scores = 3 (HR: 1.376, 95% CI: 1.031–1.836) were associated with a 1.5-fold higher likelihood of death; an NRS score 4 (HR: 1.982, 95% CI: 1.491–2.633) and NRS score ≥ 5 (HR: 1.982, 95% CI: 1.498–2.622) both evidenced a 2-fold higher likelihood of death compared with NRS score < 3. **Figure 1A** displays a positive and monotonic association between the NRS 2002 score and mortality: the higher the nutritional risk, the higher the risk of death ($P < 0.001$).

The average LoS in the group with NRS scores < 3 was 15.0 ± 10.7 days; NRS score 3 was 17.4 ± 15.2 days; NRS score 4 was 20.2 ± 21.6 days; and NRS scores ≥ 5 was 20.8 ± 17.5 (**Table 1**). Similar to the results of crude estimate analysis, after adjusting for potential covariates in the multivariable-adjusted model (**Table 2**), a higher NRS 2002 score 3 (percentage change: 16.4, 95% CI: 9.6–23.6), was associated with a significantly (16.4%) higher likelihood of increased LoS; NRS score 4 (32.4, 95% CI: 24–41.4) was associated with a 32.4% higher likelihood of increased LoS; and NRS score ≥ 5 (36.8, 95% CI: 28.3–45.8) was associated with a 36.8% higher likelihood of increased LoS compared with an NRS 2002 scores < 3. The solid lines in **Figure 1B** show that the LoS increased with the NRS 2002 score.

In **Table 1**, the mean costs in the NRS 2002 score < 3 group incurring RMB44.8 thousand (SD ± RMB45.0); NRS score 3 RMB53.5 thousand (SD ± RMB66.1); NRS score 4 RMB56.2 thousands (SD ± RMB 70.2); and NRS score ≥ 5 RMB61.9 thousand (SD ± RMB75.0). After adjusting for age, sex, education, insurance, smoking status, main disease, and CCI score covariates, **Table 2** shows that the NRS score 3 group (95% CI: 8.6–27.7) was associated with a 17.8%, the NRS score 4 group (95% CI: 19.8–43.5) a 31.1%, and the NRS score ≥ 5 (95% CI: 32.3–57.4) a 44.3%, higher likelihood of increased hospital costs compared with an NRS 2002 score < 3 group. **Figure 1C** displays the positive association between the NRS 2002 score and hospital costs, where the costs increased with nutritional risk ($P < 0.001$).

Subgroup Covariate Analysis

Mortality

For the analysis of overall mortality, **Figure 2A** shows the association between continuous NRS 2002 score and mortality among those with injury and cardiovascular system diseases was stronger than that among those with neoplasms, and diseases of the digestive system, respiratory system, and "other" diseases ($P = 0.001$), but did not differ by sex ($P = 0.410$), age ($P = 0.853$), and CCI score ($P = 0.357$). In addition, the relative risk of death from all causes was most notable among immobile older patients with injury (HR: 1.9, 95% CI: 1.5–2.4; $P < 0.001$). Also, in **Figure 3A**, the association of categorical NRS 2002 scores with mortality did not differ by sex, age, disease, and CCI score, although it appeared stronger in the diagnosis of cardiovascular system diseases, injury, and among CCI scores of 0 and 1.

Length of Stay

Concerning LoS (**Figure 2B**), the association between continuous NRS 2002 scores and LoS among those with diseases of the cardiovascular and digestive system, neoplasms, injury, and "other" diseases was stronger than that among those with diseases of the respiratory system, but did not differ by sex, age, and CCI score. The percentage change was most notable among immobile

TABLE 1 | Characteristics of 5,386 immobile Chinese older inpatients concerning NRS 2002 score on admission.

	Overall (n = 5,386)	NRS < 3 (n = 1,869)	NRS = 3 (n = 1,320)	NRS = 4 (n = 1,005)	NRS ≥ 5 (n = 1,192)	*P*-value
Vital status						<0.001
Survived	4,933 (91.6)	1,780 (95.2)	1,215 (92.0)	889 (88.5)	1,049 (88.0)	
Deceased	453 (8.4)	89 (4.8)	105 (8.0)	116 (11.5)	143 (12.0)	
Average length of stay, mean (SD)	17.8 (16.0)	15.0 (10.7)	17.4 (15.2)	20.2 (21.6)	20.8 (17.5)	<0.001
Average hospital cost (Thousands), mean (SD)	52.8 (63.1)	44.8 (45.0)	53.5 (66.1)	56.2 (70.2)	61.9 (75.0)	<0.001
Sex						0.001
Male	3,096 (57.5)	1,057 (56.6)	717 (54.3)	580 (57.7)	742 (62.2)	
Female	2,290 (42.5)	812 (43.4)	603 (45.7)	425 (42.3)	450 (37.8)	
Age						<0.001
60–69	2,698 (50.1)	1,213 (64.9)	689 (52.2)	404 (40.2)	392 (32.9)	
70+	2,688 (49.9)	656 (35.1)	631 (47.8)	601 (59.8)	800 (67.1)	
Education						0.053
Illiteracy	1,020 (18.9)	321 (17.2)	274 (20.8)	203 (20.2)	222 (18.6)	
Primary school	1,955 (36.3)	706 (37.8)	494 (37.4)	336 (33.4)	419 (35.2)	
Junior high school	1,165 (21.6)	419 (22.4)	251 (19.0)	226 (22.5)	269 (22.6)	
High school and above	1,246 (23.1)	423 (22.6)	301 (22.8)	240 (23.9)	282 (23.7)	
Insurance						<0.001
No insurance	1,049 (19.5)	419 (22.4)	256 (19.4)	185 (18.4)	189 (15.9)	
NCMS	1,603 (29.8)	537 (28.7)	427 (32.3)	292 (29.1)	347 (29.1)	
URBMI	1,168 (21.7)	364 (19.5)	272 (20.6)	217 (21.6)	315 (26.4)	
UEBMI	1,566 (29.1)	549 (29.4)	365 (27.7)	311 (30.9)	341 (28.6)	
Smoking status						<0.001
Never	3,797 (70.5)	1,296 (69.3)	965 (73.1)	728 (72.4)	808 (67.8)	
Current	755 (14.0)	308 (16.5)	170 (12.9)	118 (11.7)	159 (13.3)	
Past	834 (15.5)	265 (14.2)	185 (14.0)	159 (15.8)	225 (18.9)	
Main disease						<0.001
Circulatory system	1,697 (31.5)	553 (29.6)	497 (37.7)	331 (32.9)	316 (26.5)	
Neoplasms	1,132 (21.0)	291 (15.6)	266 (20.2)	232 (23.1)	343 (28.8)	
Injury	521 (9.7)	268 (14.3)	73 (5.5)	74 (7.4)	106 (8.9)	
Digestive system	482 (8.9)	114 (6.1)	103 (7.8)	102 (10.1)	163 (13.7)	
Respiratory system	373 (6.9)	89 (4.8)	108 (8.2)	66 (6.6)	110 (9.2)	
Other	1,181 (21.9)	554 (29.6)	273 (20.7)	200 (19.9)	154 (12.9)	
CCI score						<0.001
0	1,457 (27.1)	680 (36.4)	318 (24.1)	218 (21.7)	241 (20.2)	
1	1,450 (26.9)	482 (25.8)	418 (31.7)	276 (27.5)	274 (23.0)	
2	1,250 (23.2)	384 (20.5)	281 (21.3)	256 (25.5)	329 (27.6)	
3+	1,229 (22.8)	323 (17.3)	303 (23.0)	255 (25.4)	348 (29.2)	

Data presented as mean ± SD or frequency (%), as appropriate. NRS 2002, The Nutritional Risk Screening 2002; BMI, body mass index; CCI, Charlson comorbidity index; no insurance (patients pay all hospital fees out of pocket); New Cooperative Medical System (NCMS; covered rural residents); Urban Resident Basic Medical Insurance (URBMI; covered urban residents without a stable job); and Urban Employee Basic Medical Insurance (UEBMI; covered employed workers). Past smokers refer to at least 6 months without smoking.

TABLE 2 | The association of nutritional risk with mortality, length of stay, and hospital costs.

	Mortality, Hazard ratio (95% CI)			Length of stay, Percentage change (95% CI)			Hospital cost, Percentage change (95% CI)		
	Model 1‡	Model 2§	Model 3¶	Model 1‡	Model 2§	Model 3¶	Model 1‡	Model 2§	Model 3¶
Continuous	1.226 (1.158–1.298)	1.227 (1.158–1.299)	1.215 (1.144–1.291)	8.7 (7.2–10.3)	8.5 (7–10)	8.2 (6.6–9.7)	9.4 (7.4–11.5)	9.2 (7.2–11.2)	9.2 (7.1–11.2)
Categorical (Reference = NRS < 3)									
NRS = 3	1.566 (1.179–2.079)	1.551 (1.168–2.061)	1.376 (1.031–1.836)	16.7 (9.8–24)	16.7 (9.9–23.8)	16.4 (9.6–23.6)	19.4 (10.1–29.6)	18.7 (9.5–28.7)	17.8 (8.6–27.7)
NRS = 4	2.131 (1.611–2.820)	2.114 (1.597–2.797)	1.982 (1.491–2.633)	35.6 (26.8–45)	33.9 (25.4–43)	32.4 (24–41.4)	33.0 (21.5–45.6)	33.1 (21.7–45.5)	31.1 (19.8–43.5)
NRS ≥ 5	2.124 (1.620–2.784)	2.114 (1.611–2.774)	1.982 (1.498–2.622)	39.5 (30.8–48.8)	38.5 (30–47.5)	36.8 (28.3–45.8)	45.6 (33.6–58.7)	44.1 (32.3–56.9)	44.3 (32.3–57.4)

NRS 2002, The Nutritional Risk Screening 2002. §Model 1: adjusted for age and sex. ‡Model 2: included model 2 variables and additionally education, insurance, and smoking status. Model 3: included model 2 variables and in addition main disease, and CCI score. ¶Model 3: included model 2 variables and additionally main disease, and CCI score.

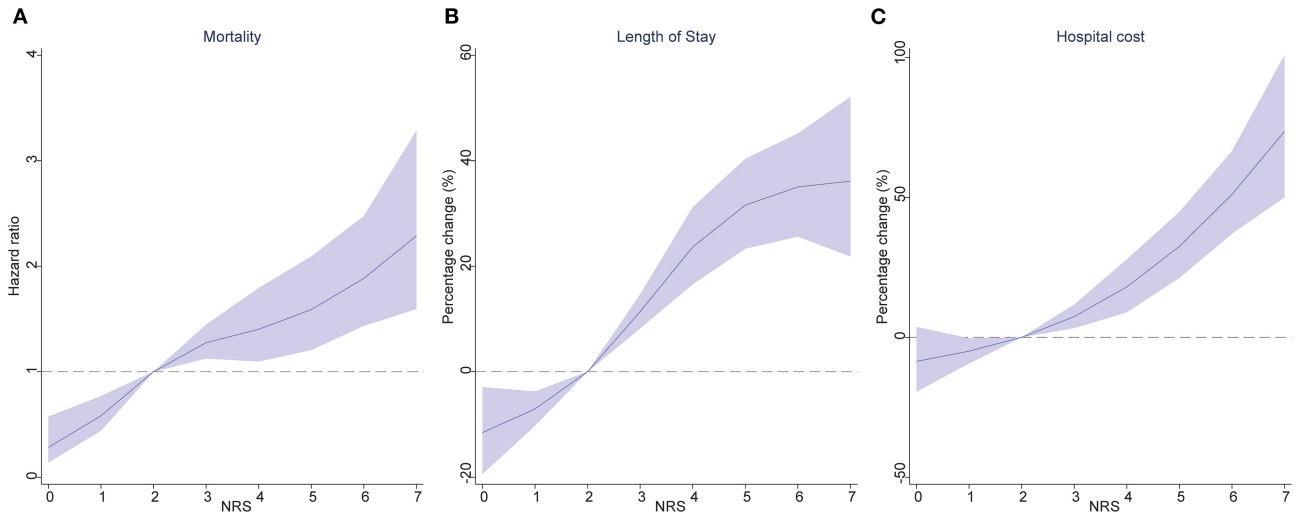

FIGURE 1 | Association of the NRS 2002 score, with mortality **(A)**, length of stay **(B)**, and hospital cost **(C)**. Hazard ratios are indicated by solid lines and 95% confidence intervals by shaded areas, reference point is NRS 2002 score = 2, with knots placed at 5th, 35th, 65th and 95th percentiles), after adjusting for age, sex, education, insurance, smoking status, main disease and CCI score. NRS 2002, Nutritional Risk Screening 2002; CCI, Charlson comorbidity index.

older inpatients with injury (10.6, 95% CI: 6.6–14.8; $P < 0.05$). In **Figure 3B**, the association of categorical NRS 2002 scores with LoS additional differ by sex, but not by age and CCI score, although it appeared stronger among patients aged 60–69 years old, and among CCI scores of 0 and 2.

Hospital Costs

As can be seen in **Figure 2C**, there was no significant association between continuous NRS 2002 scores and hospital costs, although it appeared stronger among men, among younger older patients, among those with diseases of the digestive system, injury, and "other" diseases, and among the CCI score of 0. The percentage change was most notable among immobile older inpatients with digestive diseases (13.6, 95% CI: 7.0–20.7; $P > 0.05$). In **Figure 3C**, the association of categorical NRS 2002 scores differ by age, while the association appears stronger among men, among those with injury, diseases of the digestive system, and "other" diseases, and among CCI scores of 0.

DISCUSSION

This national study is among the first to examine the burden of undernutrition in Chinese older immobile inpatients with diseases. After adjustment for covariates, nutritional risk, measured by NRS 2002, negatively impacted mortality and hospital LoS and increased the cost of hospitalization.

The prevalence of undernutrition risk, based on a positive NRS 2002 result (score ≥ 3), was 65.3% in this study. Our NRS result was the same as in Switzerland (64.6 and 62.7%) (28), but significantly higher than estimates for Denmark (23%) (35) and Brazil (48.1%) (36). The difference between the prevalence of nutritional risk reflects different nutritional risk assessment

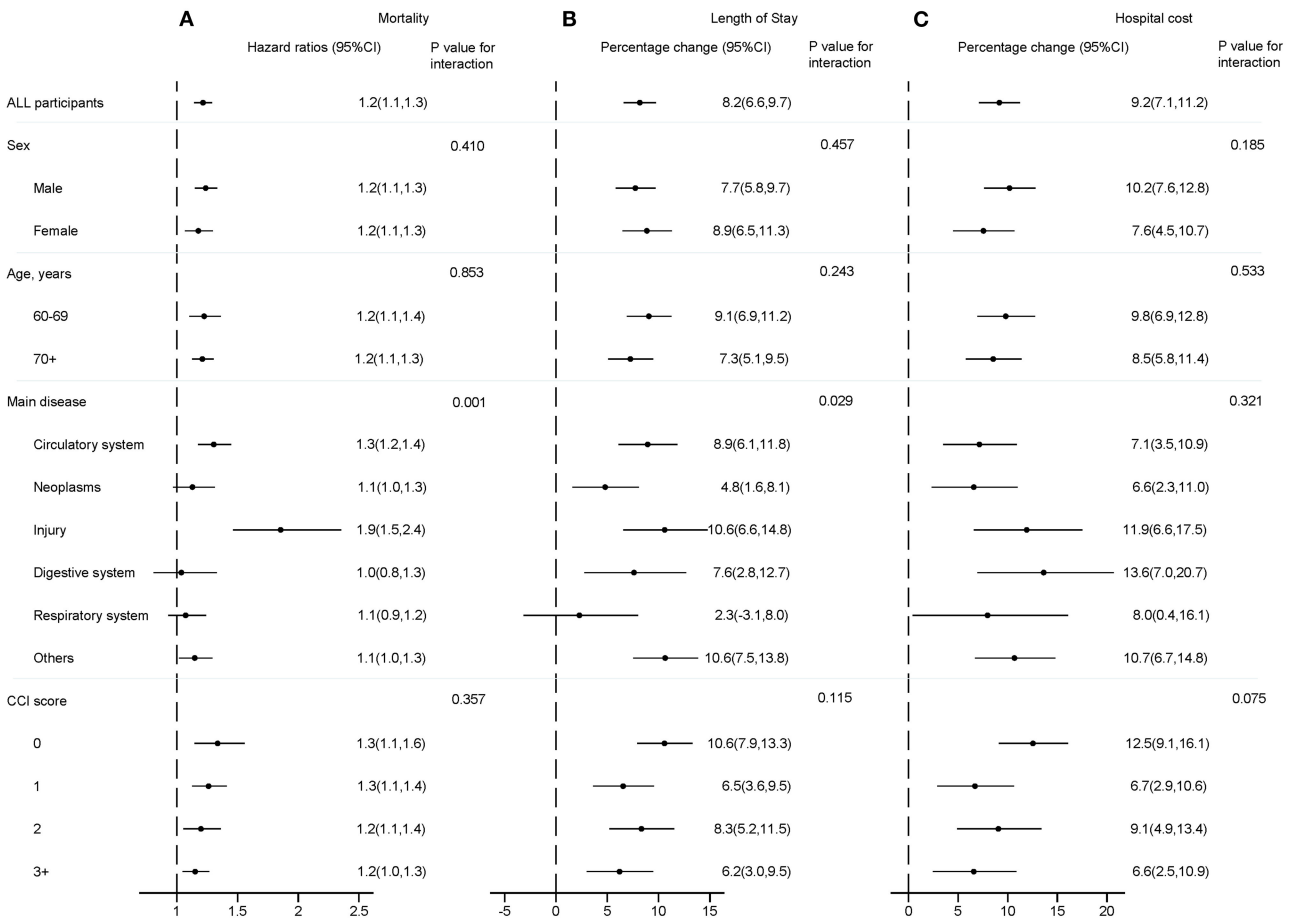

FIGURE 2 | Hazard ratios, percentage change and 95% CI for the association between the NRS 2002 score and mortality **(A)**, length of stay **(B)**, and hospital cost **(C)** adjusting for age, sex, education, insurance, smoking status, main disease and CCI score. CCI, Charlson comorbidity index; CI, confidence interval.

tools, inclusion and exclusion criteria used, and the effect of local factors, including the health system characteristics in different countries and the standards of medical treatment received (3, 4, 28, 37–40).

The association between nutritional risk and mortality has been known for some time (4, 7, 8), and our mortality rate of 8.4% saw marked differences between NRS 2002 groups ($P < 0.001$). A Swiss study of 2028 patients hospitalized in medical wards reported that nutritional risk assessed by NRS 2002 at the time of hospital admission was a good predictor of short-term (30 and 180 days) mortality, with an increased risk in mortality comparing patients scoring NRS 2002 scores of 3 with those with $\geq$ 5 points (8). These findings are in line with our results, which also show an increased risk of mortality between the NRS 2002 scores of 3 and 5+ (HR: 1.376 vs. HR: 1.982). Our results suggest that the increase in nutritional risk may be a sign of the approach of life's end among older immobile inpatients. Considering the effect of nutritional support interventions on clinical outcomes (11, 18, 41), maintaining nutritional status would be beneficial for survival among older immobile inpatients, even for those with low nutritional risk.

We also examined the association of nutritional risk and mortality, LoS, and hospital costs between different demographic characteristics, diseases, and comorbidity subgroups. Overall, we found little variation within these groups. The association between nutritional risk and mortality was not substantially different in men compared to women, 60- to 69-year-olds compared to 70+-year-olds, smokers, education level, type of insurance, and different CCI scores, suggesting that undernutrition is a risk factor across the entire immobile older inpatients population. In line with previous studies, cardiovascular system disease and injury influenced the association of nutritional risk with mortality (3, 42, 43). In the subgroup analysis, we also found that those with baseline CCI scores 0 and 1 had higher mortality related to NRS 2002 scores of 4+ compared to those with CCI scores $\geq$ 2 points. Those with baseline CCI scores of 0, 1, and 2 had higher mortality related to NRS 2002 scores of 5+ compared to those with CCI scores $\geq$ 3 points. However, the associations of nutritional risk with mortality in our study did not substantially change after adding these comorbid diseases to the models. Therefore, screening and treatment of

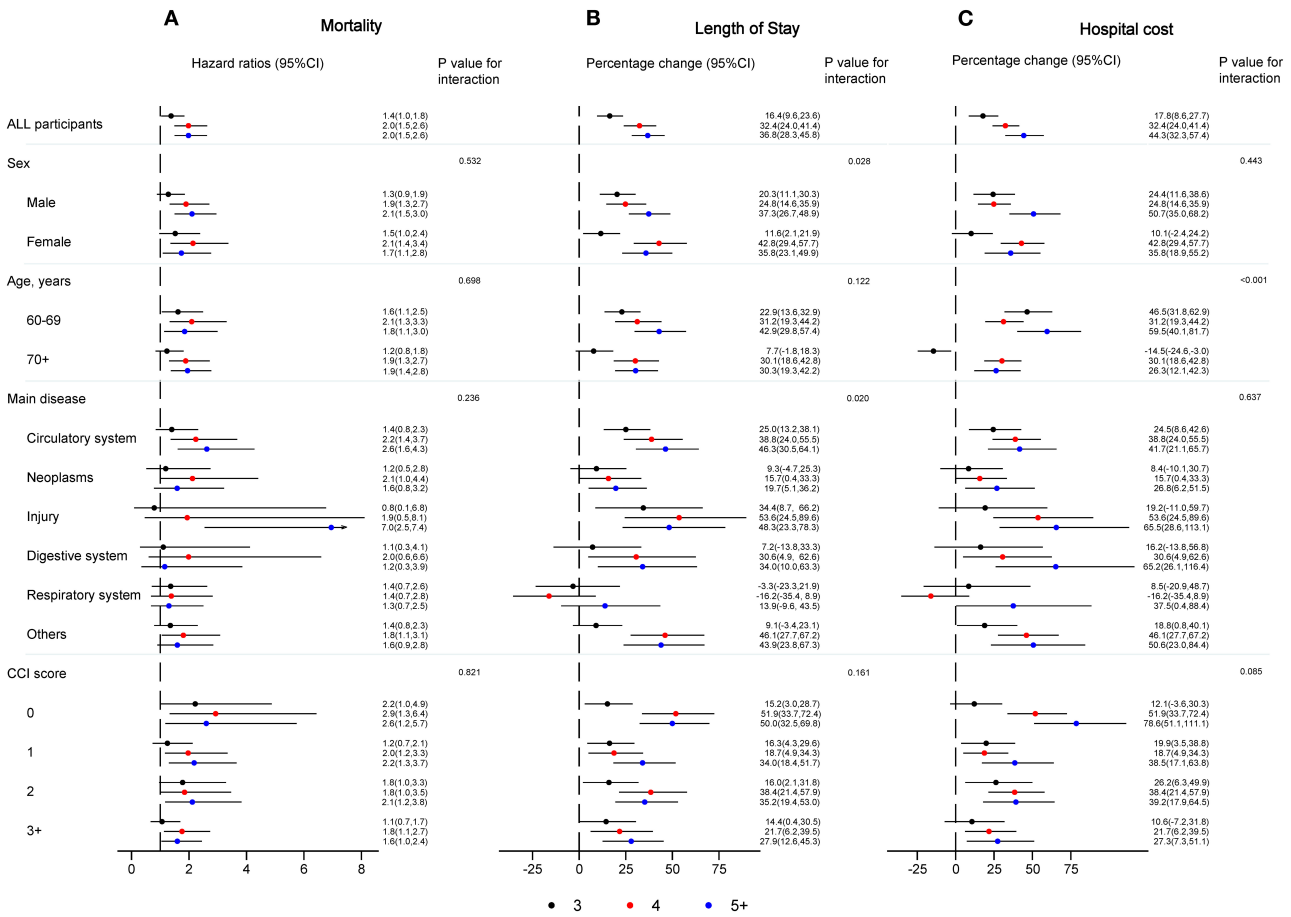

FIGURE 3 | Hazard ratios, percentage change and 95% CI for the association between NRS 2002 categories and mortality **(A)**, length of stay **(B)**, and hospital cost **(C)**, with NRS 2002 < 3 as a reference group, adjusting for age, sex, education, insurance, smoking status, main disease, and CCI score. CCI, Charlson comorbidity index; CI, confidence interval, NRS 2002, Nutritional Risk Screening 2002.

undernutrition should not be limited to patient populations with specific illnesses, but should include all hospitalized older patients. Importantly, we observed that sex influenced the association of NRS 2002 scores of 5+ with mortality, with men experiencing a higher risk of death than women (44, 45).

Specifically, subgroup analysis indicated that the most notable mortality-specific comorbidities and LoS-specific comorbidities were injuries, while the most notable cost-specific comorbidities were the diseases of the digestive system. One explanation is that approximately half of the participants were aged 70 years and older, and these patients may be unable to withstand surgical stresses, therefore patients undergoing surgical treatment due to injuries (such as fractures and peripheral nerve injuries) might increase the risk of medical complications, longer LoS, and death (46, 47). Furthermore, gastric cancer and inflammatory bowel disease are the main causes of digestive diseases among the elderly in this study, which place a significant financial burden on families of patients and the healthcare systems because of its chronicity and need for expensive therapies and surgery (48, 49).

The average LoS in patients with NRS 2002 scores < 3 was shorter than the other groups, and a statistically significant association between LoS and a positive NRS 2002 result was demonstrated in our multivariate analysis. Similar LoS findings have been reported in the United States (50), Switzerland (8), and Singapore (7), and an observational cohort study conducted in Colombia (16) reported that undernutrition at admission was independently associated with a further 1.43 LoS days after controlling for socioeconomic characteristics, disease-related factors, and medical or nursing interventions. However, the average LoS in the current study was longer than previous reports (7, 8, 16, 50), which reflects that our participants were immobile.

The association between nutritional risk and LoS was significantly different for patients with cardiovascular and digestive system diseases, neoplasms, and injury, a finding also in accordance with previous studies (3, 8, 28). Therefore, our

study strengthens the recommendation of the European Society of Parenteral and Enteral Nutrition (ESPEN) that nutritional risk screening should be performed for all hospitalized patients. In the absence of adequate screening capacities, we recommend hospitals focus on patients with cardiovascular and digestive system diseases, cancer, and injury to promote medical decision-making, save medical and nursing resources, and shorten the LoS. We also found evidence for a differing NRS 2002 scores of $\geq$ 5-LoS association between men and women, perhaps due to the sex differences in metabolic regulation among the older population, and biological sex impact on the pathogenesis of numerous diseases, such as the metabolic disorders, which is a nutritional challenge and affects clinical outcomes (51, 52).

Besides the clinical outcomes, international studies have revealed the increased hospital costs and overall economic burden associated with undernutrition in hospitals. In China, there is limited up-to-date information regarding the hospitalization costs associated with hospital undernutrition. After covariate adjustment, "at-risk" (NRS 2002 scores of 3+) older patients had higher hospital costs compared with "not-at-risk" patients (NRS 2002 scores $<$ 3). This is consistent with previous studies that reported that undernutrition could raise by 30.13% the average cost associated with hospitalization (16). Similar hospital costs findings have also been reported in Brazil (53), where the mean daily cost of care was 61% higher for the undernourished compared to well-nourished patients among 25 Brazilian hospitals.

Several studies found that early nutrition intervention for "at-risk" patients is highly cost-effective compared to delayed nutrition therapy (54–56). We recommend improved nutritional management of nutritionally "at-risk" older inpatients, for example, by issuing institutional guidelines and implementing more thorough training and enhanced collaboration between physicians, nurses, and dieticians. Developing a nutritional risk information reporting system in the HIS, which automatically notifies the clinical nutrition department to the presence of "at-risk" patients, would improve the quality of hospital care, optimize medical and nursing resources, and economize on hospital costs.

One limitation of our study was a follow-up for 90 days, with future investigations recommended undertaking observations over a longer duration to better clarify the present findings. In addition, our use of a limited number of nutritional assessment tools restricted the comparison of our results with other studies. Since our study was the first of its kind focusing on immobile older inpatients in China, few comparisons could be made to other Chinese studies. As discussed above, the participants were immobile, but the mandatory NRS 2002 tool does not include this component. We also do not have data on whether the nutritional status might worsen during the hospital stay, which might impact the evaluated health outcomes. Future Chinese studies should employ a wider range of evaluations and further assess the clinical and economic impact of nutritional interventions (such as nutritional screening and treatment) in preventing undernutrition across the different Chinese health settings. Also, future studies should develop a more detailed classification of hospital costs specifically associated with being nutritionally "at-risk." It will be of interest to further assess the different types of health expenditures, namely, the parenteral nutrition, enteral nutrition, medical treatments, nursing care, and X-rays, among nutritionally "at-risk" patients in China.

CONCLUSIONS

Early assessment, identification, and adequate management of "at-risk" undernutrition patients are warranted. Considering nutritional support can improve health outcomes and reduce healthcare costs. Greater attention to nutrition during the hospital stay and post-discharge among the older population is necessary to provide enhanced quality interventions and care for this vulnerable subpopulation.

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 Peking Union Medical College Hospital (S-700). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study concept and design by XWu. Analysis, interpretation of data, editing of the manuscript, and drafting of tables by HL and DZ. A critical review of the manuscript for important intellectual content by XWu, HL, DZ, SN, and EM. Patient recruitment, data collection, and manuscript editing by BS, JJ, YL, XWe, SC, WC, SN, and EM. All authors critically reviewed and approved the manuscript before it was submitted.

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