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Importance of body composition analysis in clinical nutrition

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Importance of body composition analysis in clinical nutrition

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Editorial: Importance of body composition analysis in clinical nutrition

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Editorial on the Research Topic
Importance of body composition analysis in clinical nutrition

Body composition analysis (BCA) refers to the description and quantification of the various components that make up the human body. Body composition (BC) can be studied at five different levels: atomic, molecular, cellular, organ and tissue, and whole body level (1). In clinical nutrition, it is critical to distinguish fat mass (FM) from fat-free mass (FFM), including skeletal muscle (SM) mass. In addition, it is important to consider the distribution of fat mass (2), acknowledging that visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) show relevant variations in structure and endocrine function and thereby have a different impact on cardiometabolic and cancer risk (3, 4). Of relevance, alterations in specific body components, such as depletion of skeletal muscle mass and loss of bone mineral density, may impact patient function and performance, as well as prognosis. BCA can be accomplished using a variety of techniques, such as anthropometric measurements, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging (US). Anthropometric measurements, including body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), calf or mid-arm circumference, and skinfold thickness, are easy to apply, inexpensive, and readily available. On the other hand, they show poor reproducibility and accuracy, and they do not necessarily reflect the distribution of body fat. BIA is a non-invasive approach that determines BC upon measurement of the electrical impedance offered by the different body compartments to the flow of an electric current. It is frequently used in clinical nutrition and allows to calculate fat mass, fat-free mass, and body cell mass (BCM) and to assess the hydration status. It is sensitive to shifts in fluid balance and is less

reliable in settings like liver, kidney, and heart failure, or electrolyte disorders. DXA is emerging as the gold standard for the evaluation of BC (5), being widely available, relatively inexpensive, and highly reproducible. DXA requires the use of a low dose of ionizing radiation but allows to measure BC at the regional and whole body level. It uses a three-compartmental model that includes bone mineral content (BMC), fat mass (FM), and lean mass (LM). MRI and CT are the most accurate methods to study BC at the organ and tissue level. However, they are expensive, time-consuming, and often not easily accessible. CT also involves a non-negligible exposure to ionizing radiation. US is a valuable tool to estimate adiposity in clinical practice, since it is non-invasive, inexpensive, and portable, and it does not imply the use of ionizing radiation (6). Nevertheless, its accuracy is operator-dependent, and standardized sonographic procedures and indices are required to improve its reproducibility. US can be used to study BC at the organ and tissue level, including measurement of visceral and subcutaneous fat thickness at defined locations, but also at the cellular level, since intracellular fat (for instance, in hepatocytes or skeletal muscle cells) is associated with increased echogenicity. It appears clear that each of the methods that can be used for BCA has both advantages and limitations, so that the most appropriate technique should be selected based on the specific context.

BCA is now becoming increasingly popular both in the research field and in clinical practice. It is particularly relevant in the field of metabolism and clinical nutrition, but its sphere of application is potentially much broader, touching virtually every specialty in medicine. BCA can be applied to the study of physiological and paraphysiological conditions—such as aging (7), growth, or adaptations to physical activity in athletes (8)—and of many different diseases including obesity, diabetes mellitus, cancer, malnutrition, and sarcopenia, providing insights into their pathophysiology. In addition, BCA can be used to assess the effects of specific interventions, such as physical exercise or nutritional therapy (9, 10). Within this Research Topic, Chao et al. explored which factors are associated with muscle health deterioration in older adults, who were followed for 6 years to assess transition from robust status to dynapenia (low muscle function with normal muscle mass), presarcopenia (low muscle mass with normal muscle function), or sarcopenia (low muscle mass and function). Older age (HR: 1.08, $p < 0.001$) and body composition parameters, especially higher fat-to-muscle ratio (FMR) determined by BIA (HR: 1.73, $p = 0.029$), were positively correlated with transition to dynapenia. By contrast, serum albumin levels were negatively correlated with transition to dynapenia (HR: 0.30, $p = 0.004$). In addition, clustering of two or more of these three factors was associated with an increased risk of transition to dynapenia, with a sort of dose-response effect. In summary, this study highlighted that older age, obesity (assessed using surrogate body composition parameters), and malnutrition (assessed using serum albumin) were the main risk factors for muscle health deterioration in healthy elderly individuals.

Jung et al. performed a cross-sectional study using BIA on 356 community-dwelling elderly individuals, who were subdivided into four categories (control, dynapenia, presarcopenia, and sarcopenia) to analyze existing differences in muscle and fat mass at the arm and leg. The study showed significant variations in body composition according to sex in the dynapenia group (reduced muscle mass at the arm and leg in women; increased fat mass at the leg in men), supporting the possibility of using different approaches to prevent this condition in males and females.

Sun J. et al. relied on BCA by whole body DXA to investigate the correlation of prediabetes and type 2 diabetes mellitus (T2DM) with adiposity in 28,429 adult patients. Their cross-sectional study found that, after adjustment for potential confounders, individuals with prediabetes or T2DM had significantly higher total percent fat (TPF), trunk fat mass, android and gynoid fat mass, and android to gynoid ratio as compared with non-diabetic individuals. In patients with T2DM, increased disease duration was associated with decreased adiposity, possibly due to therapeutic interventions. Interestingly, in patients without diabetes or with prediabetes, all body composition outcomes were directly related to serum glucose levels and glycated hemoglobin (HbA1c) levels, while significant inverse associations were found in patients with T2DM between serum glucose or HbA1c and TPF. These findings suggest that the relationship between laboratory parameters and adiposity in T2DM is complex, so that good glycemic control does not necessarily translate into improved body composition parameters.

Kerkadi et al. examined the association between bone mineral density (BMD) and body composition determined using DXA in 2,000 Qatari women, mostly obese. The study found that total lean mass was positively correlated with BMD at the spine and femur, as well as with whole body BMD and T-score. By contrast, a weak negative correlation was observed between total fat mass and femur BMD or whole body T-score. After adjusted non-linear regression, the association between parameters of fat distribution and whole body T-score was shown to be non-linear, suggesting that despite increased mechanical loading on bones, increased adiposity may not be protective against osteoporosis, but rather contribute to a decline in BMD.

Of note, the possibility of using imaging techniques for BCA sets the ground for the so-called opportunistic evaluation of body composition, which relies on the exploitation of data from scans performed for unrelated clinical reasons, and may be considerably facilitated by automatic methods (11). In this Research Topic, Van Erck et al. evaluated the use of a fully automatic method to measure psoas muscle area at the L3 level in axial CT images from patients undergoing transcatheter aortic valve replacement (TAVR), showing good agreement with the reference manual method.

A key concept in BCA is that differences in body composition may have substantial prognostic meaning (12, 13) and considerable impact on the management of patients in clinical practice. This is exemplified by several articles included in the present Research Topic. Kim et al. examined the association between volume status (in terms of edema index determined by BIA) and body composition parameters obtained by DXA/mid-thigh CT or physical performance in patients undergoing hemodialysis. Patients with high volume status had significantly decreased muscle mass (in terms of thigh muscle area index) and physical performance compared with those with low or intermediate volume status. These associations were not dependent on nutritional or inflammatory status (assessed with serum albumin and C-reactive protein levels, respectively). In addition, a high edema index was correlated with increased mortality, which might be influenced by changes in body composition and physical performance. Sun L. et al. demonstrated that overhydration is associated with an increased risk of left ventricular hypertrophy (LVH) in patients with chronic kidney disease (CKD) stage 1–4 ($n = 302$). The respective odds ratios for LVH were 3.082 ($p = 0.023$) and 4.481 ($p = 0.015$) in the middle and highest tertiles of overhydration, compared with the lowest tertile. The association was even stronger in patients with CKD stage 1–2. In addition, Xie et al. investigated the relationship between body composition parameters and hyperuricemia in 271 obese children and adolescents. Percentage of skeletal muscle (PSM) and skeletal muscle mass (SMM) determined by BIA had the strongest association with the risk of hyperuricemia (OR = 1.221 and 1.179, respectively). Hip circumference, waist circumference, and body fat mass (BFM) were also positively correlated with hyperuricemia in the whole sample of patients. However, after adjustment for age and BMI, the association between BFM and hyperuricemia was no longer detected in both boys and girls. SMM thus appears to be a better predictor of hyperuricemia compared with BFM. In the study by Xiong et al. BIA was explored as a predictor of clinical outcomes in children admitted to pediatric intensive care unit ($n = 231$). The phase angle (PhA) by BIA was found to be an independent predictor of 90-day mortality (cutoff: 3.0°), being significantly higher in survivors compared with non-survivors. There was also a weak negative correlation between PhA and duration of mechanical ventilation. Yue et al. also conducted research on critically ill children admitted to pediatric ICU ($n > 10{,}000$), uncovering a U-shaped association between serum magnesium on admission and 28-day in-hospital all-cause mortality. The lowest risk of mortality corresponded to serum magnesium levels ranging from 0.74 to 0.93 mmol/L, with levels above or below this range increasing the risk of mortality. Xu M. et al. showed that the psoas muscle index (PMI = psoas muscle area at L3 cross-section measured with CT divided by height squared) is able to predict long-term (1-year) mortality in young male patients with acute-on-chronic liver failure (ACLF), being a protective factor (HR = 0.851) at univariate COX regression analysis. In patients aged ≤ 40 years, PMI could predict 1-year mortality independently of MELD score.

Moreover, the distribution of different body components may have an impact on drug pharmacokinetics, and therefore on tolerance, toxicity, and effectiveness of pharmacological treatment. Increasing attention is now being paid to the effects of decreased fat-free mass on the pharmacokinetics of drugs (14). Given that the total amount of a drug that moves from blood into its distribution compartment (mainly fat mass for lipophilic drugs and fat-free mass for hydrophilic drugs) depends on the size of this compartment, drug distribution will be affected by body composition. When a drug is administered to a patient with its relative distribution compartment smaller than normal, for instance a sarcopenic patient, the peak plasma concentration will be higher and the time for clearance lower than normal, leading to potentiated but shorter pharmacological effects (15). In these conditions, toxicity could be increased even in the setting of decreased clinical efficacy. Evidence in support of this concept is provided by the study from Ando et al. who investigated the prognostic significance of body composition parameters determined using CT in patients with Crohn's disease before the beginning of anti-TNF therapy. Their study demonstrated that clinical outcomes at 5 years from induction of anti-TNF therapy were significantly worse in patients with lower skeletal muscle index (SMI) or mesenteric fat index (MFI = ratio of visceral to subcutaneous fat area at L3 level) compared with patients with higher SMI or MFI, respectively. A second paper focusing on patients with Crohn's disease is the one by Li et al. who reported that the GLIM (Global Leadership Initiative on Malnutrition) criteria, which include body composition parameters, may be more appropriate to assess the nutritional status in patients with Crohn's disease, as compared with screening with the NRS-2002 (Nutrition Risk Screening) tool.

It must be kept in mind that body composition analysis is inherently complex, given the large interindividual and interethnic variability that exists in both physiological and pathological conditions. This explains why numerous standardized criteria and parameters have been proposed in literature for BCA. At present, some of these are still debated and subject to change. Xu Z. et al. compared the performance of two screening methods (SARC-F and SARC-CalF) for the detection of sarcopenia in adult patients ($n = 689$) with T2DM. They concluded that SARC-CalF (strength, assisting with walking, rising from a chair, climbing stairs, and calf circumference) had enhanced sensitivity and improved overall detection of sarcopenia as compared with SARC-F (SARC + falling). Ge et al. instead determined the optimal cutoffs for the diagnosis of sarcopenia in the older Chinese population, including those for low appendicular skeletal muscle index (ASMI) by BIA, low handgrip strength, and

low gait speed. In addition, Scafoglieri et al. examined the relationship between VAT distribution ratios (VAT/SAT and VAT/SM) and anthropometric indices commonly used in clinical practice to evaluate BC, including WHR and WC, in a multi-ethnic population ($n = 419$). In both sexes, VAT distribution ratios were shown to have non-linear associations with age and with anthropometric measurements. These findings are relevant in that they suggest that the interpretation of changes in body composition cannot simply rely on linear extrapolations.

The present Research Topic collection also includes: an interesting review on the pathology and physiology of ileostomy (Ma et al.), which is associated with significant structural, functional, and microbiological changes at the intestinal level; a randomized controlled trial showing that individualized nutritional support in hospitalized patients with oropharyngeal dysphagia after stroke may improve swallowing function and maintenance of nutritional status during the first week of hospitalization (Yan et al.); and a systematic review and meta-analysis on the efficacy of glutamine supplementation in the treatment of severe acute pancreatitis (Dong et al.).

To conclude, as supported by the evidence included in this Research Topic, body composition analysis is emerging as a valuable instrument for the study and clinical evaluation of several different diseases, especially in the field of clinical nutrition and metabolism. Importantly, body composition parameters may have predictive and prognostic values as well as a strong impact on patient management.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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

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ORIGINAL RESEARCH
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Psoas Muscle Index Can Be Used to Predict Long-Term Mortality in Young Male Patients With Acute-on-Chronic Liver Failure

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Objective: The use of psoas muscle index (PMI) in acute-on-chronic liver failure (ACLF) has not been reported, and the aim of this study was to evaluate the predictive value of PMI for the prognosis of patients with ACLF.

Methods: In this study, male ACLF patients who underwent abdominal CT between 2015 and 2019 in our center were included to analyze the association between PMI and 1-year mortality in male ACLF patients, and subgroup analyses were performed according to age stratification (≤40 and >40 years).

Results: We included 116 male patients with confirmed ACLF, with a mean PMI of 5.98 ± 1.68 cm^2/m^2 and a 1-year mortality of 51.7% (60). Univariate COX regression analysis showed that PMI was a protective factor [hazard ratio (HR), 0.851, 95%CI: 0.734–0.987] for 1-year mortality in male patients with ACLF. Nevertheless, multivariate analysis did not find an independent relationship between PMI and 1-year mortality. Subgroup analysis by age found that adjusted for MELD score, PMI was independently associated with 1-year mortality in young (age ≤ 40 years) male patients with ACLF (HR 0.689, 95% CI: 0.496–0.958). While no effect of PMI on 1-year mortality in non-young (age > 40 years) male ACLF patients was found. Correlation analysis found that there was no significant correlation between PMI and age in young (age ≤ 40 years) male ACLF patients, but, PMI decreased with age ($r = -0.246$, $P < 0.05$) in non-young (age > 40 years) male ACLF patients.

Conclusion: PMI was found to be associated with 1-year mortality in male ACLF patients, especially in patients younger than 40 years, PMI predict 1-year mortality independent of MELD score.

Keywords: psoas muscle index, acute-on-chronic liver failure, long-term outcome, male, prognosis

INTRODUCTION

The evaluation of nutritional status of patients with chronic liver disease by muscle mass and muscle function is receiving more and more attention. Sarcopenia is a major feature of malnutrition in patients with liver disease and is an important indicator affecting the prognosis of patients with end-stage liver disease (ESLD) (1). Numerous studies (2–5) have used the skeletal muscle index at the third lumbar vertebrae (L3-SMI) to determine sarcopenia, to further evaluate the association between sarcopenia and the prognosis of patients with chronic liver disease (CLD), and also some studies have evaluated the impact of the psoas muscle index (PMI) on the prognosis of CLD (6, 7). Studies (8–11) have shown that sarcopenia can be valuable as a predictor of disease progression, complications of cirrhosis such as the incidence of hepatic encephalopathy, mortality of cirrhotic patients, long-term outcome after liver transplantation, and outcome of patients with HCC.

Acute-on-chronic liver failure (ACLF) is a clinical syndrome manifested by acute liver decompensation in chronic liver disease (12) with rapid disease progression and high case fatality rate, and active exploration of indicators determining prognosis is valuable to guide treatment. This research team evaluated the predictive value of L3-SMI and sarcopenia for 90 day mortality in ACLF patients and found that sarcopenia had limited predictive value for the prognosis of ACLF (13) due to the heterogeneity of cut-off values for L3-SMI in diagnosing sarcopenia. Study (14) has shown that PMI is positively correlated with L3-SMI and is able to predict long-term prognosis in patients with cirrhosis (6).

As far as we can determine, there is a paucity of data exploring exploring the relationship between PMI and long-term outcomes in ACLF patients. Overall, this study aimed (1) to analyze the relationship between PMI and 1-year mortality in male ACLF patients and (2) to elucidate the effect of PMI on 1-year mortality risk in male ACLF patients in different age subgroups.

METHODS

Patients

Patients with ACLF aged ≥18 years, who were hospitalized in Beijing You'an Hospital between January 2015 to June 2019, were retrospectively enrolled for the current study. Patients who met the following criteria were included: (1) 18 years of age or older; (2) underwent abdominal CT within 2 weeks of hospitalization; (3) diagnosed with ACLF according to the relevant diagnostic criteria of the Asian Pacific Association for the Study of the Liver (APASL) (15), manifested by jaundice (total bilirubin [TB] ≥ 5mg/dL) and coagulation dysfunction (international normalized ratio[INR] ≥ 1.5), and complicated within 4 weeks by ascites and/or hepatic encephalopathy (HE).

The exclusion criteria were as follows: (1) complicated by hepatocellular carcinoma (HCC) or other malignant tumors; (2) end stage disease of extrahepatic organs, such as respiratory failure or heart failure; (3) complicated by other consumptive diseases, such as tuberculosis or hyperthyroidism; (4) patients with neuromuscular diseases and those who were long-term bedridden; and (5) patients who had undergone long-term corticosteroid treatment.

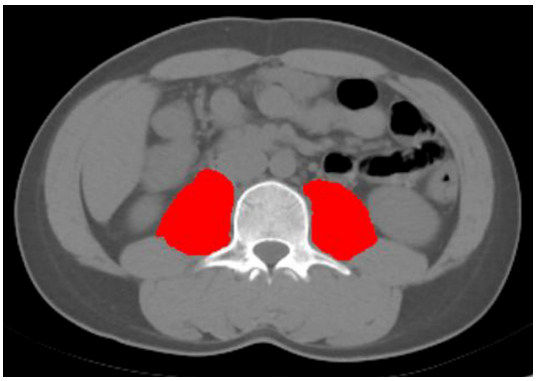

FIGURE 1 | The psoas muscle mass area at the level of L3 vertebra.

All patient data were retrieved from electronic medical records. Follow-up was documented for 360 days after admission. The study procedures were approved by the Ethics Committees of Beijing You'an Hospital. As this was a retrospective study, informed consent was waived.

Clinical Data

Clinical and laboratory results during the patients' hospitalization were collected, including sex, age, height, body mass, and complications, such as ascites and hepatic encephalopathy. Laboratory data were also collected at the diagnosis of ACLF, including routine blood tests, liver function, renal function, electrolytes and coagulation related indices.Information on liver transplantation and death were also collected for all enrolled patients and transplant-free survival/mortality was estimated for all enrolled patients at 360 days after enrollment or ACLF diagnosis. The patients' Model End-Stage Liver Disease (MELD) scores were calculated.

ACLF patients often have body fluid retention such as edema and ascites. In this study, the dry weight of ACLF patients with body fluid retention was calculated and corrected according to the clinical severity of ascites minus a certain amount of body weight (16) (mild 5%, moderate 10%, severe 15%, and 5% if there was peripheral edema). The body mass index (BMI) was calculated according to the following formula: BMI = dry weight (kg) / height squared (m^2), and a BMI ≥ 25 kg/m^2 was recognized as obesity in accordance with the BMI assessment criteria in China.

Assessment of Psoas Muscle Index

Abdominal CT examinations were performed in all patients within 2 weeks of diagnosis of ACLF. CT scanning was performed with the LightSpeed VCT CT 64 scanner, USA. Psoas muscle area (cm^2): the cross-sectional area (cm^2) of the right and left psoas muscle at the third lumbar level (L3) on CT imaging estimates human skeletal muscle content (**Figure 1**). The psoas

TABLE 1 | Baseline characteristics of surviving vs. non surviving patients in male acute-on-chronic liver failure.

Variables	Total ($n = 116$)	Survivors ($n = 60$)	Non-survivors ($n = 56$)	*p*
Age (years)	43.64 ± 10.43	40.88 ± 10.46	46.55 ± 9.66	0.003
Cirrhosis	71 (61)	27 (45)	44 (79)	< 0.001
BMI (kg/m^2)	22.81 (20.48, 24.28)	22.98 (20.66, 24.44)	22.63 (20.24, 24.19)	0.510
Obesity	37 (32)	22 (37)	15 (27)	0.346
ALB (g/L)	29.95 ± 5.54	30.06 ± 5.25	29.84 ± 5.88	0.831
TB (mg/dL)	21.85 (14.67, 29.18)	18.10 (11.00, 23.90)	26.50 (19.03, 32.18)	<0.001
INR	2.40 (2.10, 3.16)	2.26 (2.07, 2.66)	2.88 (2.12, 3.36)	0.006
CR (mg/dL)	0.70 (0.58, 0.83)	0.69 (0.56, 0.83)	0.71 (0.61, 0.82)	0.409
Na (mmol/L)	135.50 (131.70, 138.00)	136.90 (134.07, 138.83)	134.40 (130.15, 135.95)	<0.001
WBC (*10^9/L)	6.97 (5.03, 9.80)	6.73 (5.20, 9.73)	7.32 (4.98, 9.50)	0.718
PLT (*10^9/L)	96.00 (64.00, 149.00)	106.50 (74.00, 149.50)	82.00 (60.50, 139.00)	0.149
HGB (g/L)	121.15 ± 24.76	123.95 ± 23.62	118.15 ± 25.80	0.215
MELD score	24.34 (19.65, 26.95)	22.27 (18.48, 25.09)	26.04 (22.80, 28.58)	<0.001
Ascites	91 (78)	40 (67)	51 (91)	0.003
HE	27 (23)	8 (13)	19 (34)	0.016
PMI (cm^2/m^2)	5.98 ± 1.68	6.38 ± 1.77	5.56 ± 1.48	0.007

Data were expressed as mean ± standard deviation, median (interquartile range), proportions or simple frequencies as appropriate. BMI, body mass index; ALB, albumin; TB, total bilirubin; INR, International normalized ratio; CR, Serum creatinine; Na, Serum sodium; WBC, White blood cell count; PLT, platelet; HGB, hemoglobin; MELD, model for end-stage liver disease; HE, Hepatic encephalopathy; PMI, psoas muscle index.

muscle area of the L3 cross-section was evaluated by two imaging physicians independently. When disagreement occurred, a third physician was involved and an agreement was reached.The psoas muscle index was calculated as the area of psoas muscle at the L3 level divided by the square of height (m^2) to obtain the PMI (17).

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) in the case of parametric data distribution or median (interquartile range (IQR)) in the case of non-parametric data distribution. Categorical variables are presented as a percentage. The Student's t-test was used for group comparisons of parametric data, while the Mann-Whitney-U test was used for non-parametric data. Group comparisons of categorical variables were performed using the $\chi 2$ test. Inter- and intra-observer agreement over the area of the psoas muscle were determined using the intraclass correlation coefficient (ICC). Clinical characteristics associated with mortality in ACLF patients were assessed using Multivariate Cox proportional hazards (PH) model,which were fitted with a stepwise method using significant baseline factors (candidate variables included PMI, complications and laboratory measurements, $p < 0.05$) that had been prefiltered in univariate PH models to identify the independent relationship between PMI and mortality of patients with ACLF. Pearson correlation was used to analyze the correlation between age and PMI. *P*-values less than 0.05 were regarded as significant for 2-sided tests. All statistical analyses were performed with R × 64 4.0.3 (http://www.r-project.org/) GraphPad Prism Version 8.0 (GraphPad Software, La Jolla, CA, USA).

RESULTS

Characteristics of the Patients

In the present study, we included 116 male patients with confirmed ACLF at a mean age of 43.64 (SD ± 10.43) years, including 61.0% (71) patients with cirrhosis. The most common etiology of ACLF was viral hepatitis (71.6%), followed by alcohol (17.2%). Overall, the median BMI in the study patients was 22.81 (20.48, 24.28) kg/m^2, with 32.0% being obese (**Table 1**), and the median MELD scores was 24.34 (19.65, 26.95). For the measurement of psoas muscle area, a high intra-observer (ICC = 0.998, $p < 0.001$) and inter-observer agreement (ICC = 0.994, $p < 0.001$) were observed.The PMI of male patients with ACLF was 5.98 ± 1.68 cm^2/m^2.

Baseline Characteristics of Surviving vs. Non-surviving Patients in Male ACLF

Of the 116 male ACLF patients, 60 (51.7%) patients were alive at 360 days (survivors), 51 patients died and 5 underwent liver transplantation (non survivors). Demographics, laboratory data, MELD scores and complications were compared between survival and non-survival patients with ACLF (**Table 1**). The mean age of patients in the male ACLF survival group was 40.88 ± 10.46 years, which was significantly lower than that of the non-survival group (46.55 ± 9.66 years) ($P = 0.003$); The proportion of cirrhotic patients in the non-survival group (79%) was significantly higher than that in the survival group (45%), and the difference was statistically significant.Total bilirubin, INR, MELD score were significantly higher and serum sodium level was significantly ($P < 0.05$) lower in the non-survival group compared to the survival group. The PMI of the surviving group

TABLE 2 | Univariate and multivariate COX regression models for male patients with ACLF.

Variables	Univariate		Multivariate	
	HR (95% CI for HR)	p.value	HR (95% CI for HR)	p.value
Age (years)	1.040 (1.010–1.060)	0.004		
Cirrhosis	2.820 (1.490–5.350)	0.002	2.746 (1.229–6.136)	0.014
BMI (kg/m^2)	0.983 (0.918–1.050)	0.615		
Obesity	0.734 (0.406–1.330)	0.306		
ALB (g/L)	1.000 (0.956–1.050)	0.915		
TB (mg/dL)	1.050 (1.030–1.070)	0.000	1.041 (1.016–1.067)	0.001
INR	2.390 (1.570–3.630)	0.000	2.800 (1.798–4.363)	0.000
CR (mg/dL)	1.160 (0.642–2.110)	0.616		
Na (mmol/L)	0.912 (0.866–0.960)	0.000		
WBC (*10^9/L)	0.987 (0.949–1.030)	0.533		
PLT (*10^9/L)	0.997 (0.993–1.000)	0.191		
HGB (g/L)	0.992 (0.982–1.000)	0.163		
MELD score	1.100 (1.040–1.160)	0.000		
Ascites	3.630 (1.450–9.110)	0.006	4.902 (1.152–20.858)	0.031
HE	1.840 (1.060–3.210)	0.031		
PMI (cm^2/m^2)	0.851 (0.734–0.987)	0.033		

The multivariate logistic regression model was fited with a stepwise selection method using statistically baseline factors that had been screened in univariate analysis. BMI, body mass index; ALB, albumin; TB, total bilirubin; INR, International normalized ratio; CR, Serum creatinine; Na, Serum sodium; WBC, White blood cell count; PLT, platelet; HGB, hemoglobin; MELD, model for end-stage liver disease; HE, Hepatic encephalopathy; PMI, psoas muscle index.

patients was significantly lower than that of the non-surviving group patients [5.56 ± 1.48 cm^2/m^2 vs. 6.38 ± 1.77 cm^2/m^2, $P = 0.007$]. In addition, no significant difference was observed in the incidence of predisposing factors between patients with ACLF who survived and those who did not (**Supplementary Table 1**).

PMI and Long-Term (360 Days) Mortality in Male Patients With ACLF

To clarify the independent relationship between PMI and long-term outcomes in male patients with ACLF, we performed univariate and multivariate Cox regression analyses of patients at 360 days of follow-up (**Table 2**). Univariate COX regression analysis showed that age, liver cirrhosis, total bilirubin, INR, lower serum sodium, MELD score, ascites and HE were risk factors for 360 day mortality in male patients with ACLF, while

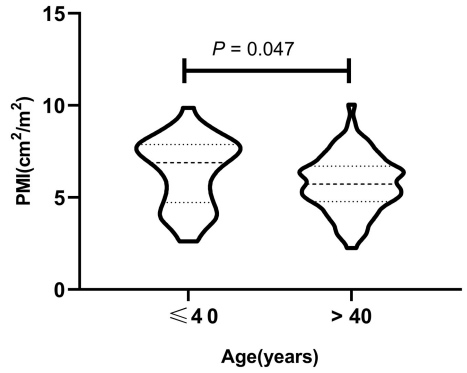

FIGURE 2 | The psoas muscle index (PMI) in different age subgroups in male ACLF patients.

PMI was its protective factor (hazard ratio (HR), 0.851, 95%CI: 0.734–0.987) ($P < 0.05$).

When the above variables were included in the multivariate COX regression model, it was found that cirrhosis (HR, 2.746, 95%CI: 1.229–6.136),TB (HR, 1.041, 95%CI: 1.016–1.067), INR (HR, 2.800, 95%CI: 1.798–4.363) and ascites (HR, 4.902, 95%CI: 1.152–20.858) were risk factors for 360 day mortality in male patients with ACLF ($P < 0.05$). Nevertheless, multivariate analysis did not find an independent relationship between PMI and 360 day mortality in male ACLF patients.

PMI in Male ACLF Patients of Different Age Subgroups

Skeletal muscle mass decreases gradually with age, and previous studies (17, 18) have shown that muscle mass decreases gradually from approximately age 40. Therefore, in this study, male ACLF patients were divided into two groups according to age: ≤40 and >40. The median PMI of the two groups were 6.89 (4.73–7.88) and 5.73 (4.78–6.70) cm^2/m^2, respectively, with significant differences (**Figure 2**) ($P < 0.05$). Univariate Cox regression analysis found an interaction effect of PMI * age (≤40 and >40 years) on 360 day mortality in male ACLF patients [0.647 (0.447–0.936), $P = 0.021$], so further subgroup analysis by age was performed in this study.

PMI and Long-Term (360 Days) Mortality in Young (Age ≤ 40 Years) Male Patients With ACLF

A total of 41 male ACLF patients aged ≤ 40 years had a 360 day mortality rate of 29.3% (12), and the comparison between the survival and non survival groups was detailed in **Supplementary Table 2**. The median PMI of young male ACLF patients in the survival group was 7.34 (5.32, 7.97) cm^2/m^2, which was significantly higher than that of non-survival patients [5.47 (4.19, 6.46) cm^2/m^2, $P = 0.014$].

Following univariate Cox regression analysis of patients' clinical characteristics, TB, INR, MELD score, serum sodium and HE were significantly associated with mortality in patients with cirrhosis (**Table 3**), and low PMI is associated with increased 360 day mortality in young male ACLF patients [0.745 (0.557–0.997),

TABLE 3 | Univariate and multivariate Cox regression models in young (age ≤ 40 years) male ACLF patients.

Variables	Univariate		Multivariate	
	HR (95% CI for HR)	p.value	HR (95% CI for HR)	p.value
Age (years)	1.040 (0.932–1.160)	0.493		
Cirrhosis	3.360 (0.910–12.400)	0.069		
BMI (kg/m^2)	0.977 (0.856–1.120)	0.730		
Obesity	0.927 (0.294–2.920)	0.897		
ALB (g/L)	0.942 (0.858–1.030)	0.205		
TB (mg/dL)	1.070 (1.010–1.130)	0.021		
INR	3.880 (1.610–9.380)	0.003		
CR (mg/dL)	5.460 (0.283–105.000)	0.261		
Na (mmol/L)	0.859 (0.783–0.941)	0.001		
WBC (*10^9/L)	0.955 (0.859–1.060)	0.391		
PLT (*10^9/L)	0.991 (0.980–1.000)	0.088		
HGB (g/L)	0.982 (0.961–1.000)	0.088		
MELD score	1.430 (1.190–1.720)	0.000	1.381 (1.137–1.676)	0.001
Ascites	0.025 (0.000–3.770)	0.150		
HE	3.700 (1.170–11.700)	0.026		
PMI (cm^2/m^2)	0.745 (0.557–0.997)	0.048	0.689 (0.496–0.958)	0.027

The multivariate logistic regression model was fited with a stepwise selection method. Considering that there are too few dependent variables in our study, to avoid over fitting the model, according to the previous research results and clinical constraints, select MELD and PMI for multivariate analysis. BMI, body mass index; ALB, albumin; TB, total bilirubin; INR, International normalized ratio; CR, Serum creatinine; Na, Serum sodium; WBC, White blood cell count; PLT, platelet; HGB, hemoglobin; MELD, model for end-stage liver disease; HE, Hepatic encephalopathy; PMI, psoas muscle index.

$P = 0.048$]. Considering that there are too few dependent variables in our study, to avoid over fitting the model, according to the previous research results and clinical constraints, select MELD and PMI for multivariate analysis. The results showed that PMI was a factor affecting 360 day mortality in young male ACLF patients independently of MELD score (HR 0.689, 95%CI: 0.496–0.958).

PMI and Long-Term (360 Days) Mortality in Non-young (Age > 40 Years) Male Patients With ACLF

The 360 day mortality rate of 75 non-young male ACLF patients in this study was 58.67%, and the baseline characteristics of the patients between the survival and non-survival groups was detailed in **Supplementary Table 3**. The mean PMI of ACLF patients in survival group and non survival group were 5.99 ± 1.58 and 5.60 ± 1.50 cm^2/m^2, respectively, and the difference did not show statistical significance ($P = 0.290$). The univariate Cox regression analysis similarly did not find an independent relationship between PMI and the risk of 360 day mortality in non-young male ACLF patients. Multivariate Cox regression analysis identified TB and INR as independent risk factors for 360 mortality in non-young male ACLF patients (**Table 4**).

TABLE 4 | Univariate and multivariate Cox regression models in non-young (age > 40 years) male ACLF patients.

Variables	Univariate		Multivariate	
	HR (95% CI for HR)	p.value	HR (95% CI for HR)	p.value
Age (years)	1.020 (0.973–1.060)	0.471		
Cirrhosis	2.260 (1.09–4.720)	0.029		
BMI (kg/m^2)	1.010 (0.927–1.100)	0.852		
Obesity	0.826 (0.408–1.670)	0.595		
ALB (g/L)	1.030 (0.977–1.090)	0.271		
TB (mg/dL)	1.040 (1.020–1.070)	0.000	1.048 (1.022–1.074)	0.000
INR	1.950 (1.200–3.150)	0.007	1.921 (1.171–3.152)	0.010
CR (mg/dL)	0.893 (0.449–1.780)	0.747		
Na (mmol/L)	0.948 (0.887–1.010)	0.110		
WBC (*10^9/L)	1.030 (0.972–1.080)	0.362		
PLT (*10^9/L)	1.000 (0.995–1.000)	0.847		
HGB (g/L)	1.000 (0.987–1.010)	0.960		
MELD score	1.040 (0.991–1.100)	0.104		
Ascites	0.502 (0.198–1.276)	0.148		
HE	1.640 (0.845–3.200)	0.143		
PMI (cm^2/m^2)	0.946 (0.786–1.140)	0.555		

The multivariate logistic regression model was fited with a stepwise selection method using statistically baseline factors that had been screened in univariate analysis. BMI, body mass index; ALB, albumin; TB, total bilirubin; INR, International normalized ratio; CR, Serum creatinine; Na, Serum sodium; WBC, White blood cell count; PLT, platelet; HGB, hemoglobin; MELD, model for end-stage liver disease; HE, Hepatic encephalopathy; PMI, psoas muscle index.

Correlation Between PMI and Age in Male ACLF Patients of Different Age Subgroups

To explore the reasons for the differences in the PMI effects on mortality in different age subgroups, we performed the correlation between PMI and age in different age subgroups

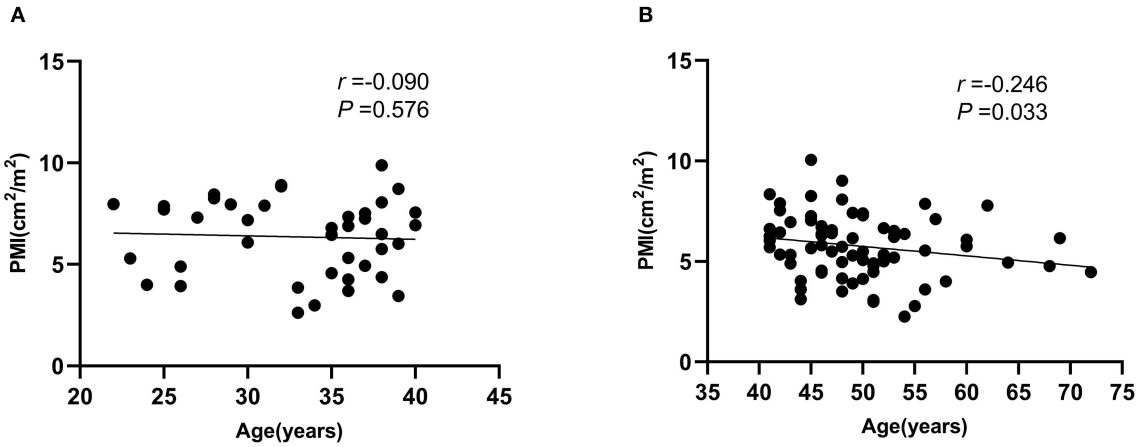

FIGURE 3 | Correlation between psoas muscle index (PMI) and age in different age subgroups in male ACLF patients. **(A)** Age ≤ 40 years, **(B)** Age > 40 years.

(**Figure 3**), which showed that there was no significant correlation between PMI and age in young (age ≤ 40 years) male ACLF patients, however, there was a negative correlation between PMI and age in non-young (age > 40 years) male ACLF patients, which decreased with age ($P < 0.05$).

DISCUSSION

This study is the first to explore the effect of PMI on long-term outcomes (1 year) of ACLF patients, and the results found that PMI could distinguish 1-year survival from death in male ACLF patients. Found in different age subgroup analyses that for young male ACLF patients under 40 years old, PMI could predict 1-year mortality independently of MELD score, but for male ACLF patients over 40 years old, PMI was more affected by increasing age and had limited predictive value for 1-year mortality.

The predictive value of sarcopenia in chronic liver disease has been paid more and more attention (7, 19). Recently, a meta-analysis (20) confirmed that sarcopenia was highly and independently associated with higher risk of mortality in patients with cirrhosis, which was consistent with a large sample multicenter study in China (21). In addition, studies (22, 23) have reported that sarcopenia increases the risk of progression to ACLF and mortality in cirrhotic patients receiving transjugular intrahepatic portosystemic shunt. However, most studies have used SMI as a criterion to evaluate sarcopenia, and very few studies have evaluated the predictive prognostic value of PMI in chronic liver diseases. A multicenter study (24) that evaluated the prognostic impact of SMI vs. PMI in cirrhotic patients showed that SMI is a more complete and reliable measure than PMI, especially in male cirrhotic patients, and patients at high risk of mortality as determined by SMI were misclassified as low risk of mortality by the PMI cut-off value, so the investigators concluded that SMI should not be replaced by PMI. On the contrary, our scholars (6) developed a prognostic model that included the PMI through the long-term follow-up of cirrhotic patients, and the results showed that the PMI was an independent predictor of the 3-year mortality risk of cirrhotic patients and that the PMI was associated with the gait speed of the patients. The c-index of the predictive model that included the PMI was 0.792 (95% CI: 0.723–0.861) in men and 0.715 (95% CI: 0.637–0.793) in women, respectively, implying that a prediction model containing PMI can predict long-term mortality in cirrhotic patients with high efficiency. An additional study (25) evaluating the impact of PMI on outcomes after liver transplantation demonstrated that the 120 day survival rate after liver transplantation was significantly lower in the lower PMI preoperative group than in the higher PMI group, that there was a significant association between preoperative PMI and short-term postoperative outcomes, and that sarcopenia estimated by PMI could be used as a predictor of mortality risk after liver transplantation. Another study that used PMI to diagnose sarcopenia found that sarcopenia was associated with post-transplant infections, requirement for mechanical ventilation, intensive care (ICU) and hospital stay, and 1 year mortality in liver transplant recipients (26).

Currently, most of the reported predictive values of PMI in CLD have focused on patients undergoing liver transplantation, cirrhotic patients. The present study confirmed the value of PMI in predicting the long-term prognosis of ACLF, especially for young male ACLF patients, and showed a higher predictive value than SMI compared with the results of previous study (13), which may have several reasons: First, the SMI was based on the whole skeletal muscle area at the cross-section of the third lumbar body, while the PMI was based on the sum of the areas of the right and left psoas muscles at the third lumbar paraspinal body with less systematic error and better accuracy. Second, the predictive value of the PMI for prognosis in ACLF in men over 40 years of age was not found in this study, and for this part of the population, the decline in skeletal muscle mass was more influenced by increasing age, while the association with muscle wasting due to liver failure is not strong, and the specific mechanism still needs further validation in a large sample multicenter prospective study. A retrospective cohort study (27) of pediatric end-stage liver disease patients who underwent liver transplantation found

that lower PMI were associated with higher reoperation rates and longer posttransplant hospital stays. It is thus speculated that the PMI has more value in judging prognosis in young patients with liver disease.

In addition to its retrospective design, there are some limitations in this study. First, only male ACLF patients were included in this study, and the sample size was small, especially in different age subgroups. Second, this study only evaluated the PMI at baseline in ACLF patients and did not evaluate the dynamic changes of PMI during the course of ACLF, so the effect of PMI on the prognosis of ACLF was not fully evaluated. However, the current study is the first to evaluate the value of PMI in ACLF and provides a reference for further research.Third, this study evaluated the long-term outcomes of patients with ACLF and only analyzed the impact of baseline data on outcomes and did not consider the impact of treatment regimen and patient compliance on outcomes. Finally, the mechanism of muscle mass wasting in ACLF patients was not elucidated in this study, which is our next focus.

In conclusion, in our study cohort, PMI was found to be associated with 1-year mortality in male ACLF patients, especially in patients younger than 40 years, PMI predict 1-year mortality independent of MELD score. The value of PMI in ACLF needs additional basic research and larger clinical studies to clarify.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Beijing You'an Hospital. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

YC: conceptualization and supervision. MX, TL, MK, GG, and YC: methodology, formal analysis, visualization, and writing—original draft. MX, TL, and WS: resource. MX, TL, YH, ZD, WS, and YC: data curation and writing—review and editing. All authors have made an intellectual contribution to the manuscript and approved the submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.811826/full#supplementary-material

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A Novel U-Shaped Association Between Serum Magnesium on Admission and 28-Day In-hospital All-Cause Mortality in the Pediatric Intensive Care Unit

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Objective: Our purpose is to evaluate whether serum magnesium when entering the ICU is related to 28-day in-hospital all-cause mortality in the pediatric ICU.

Methods: We used the PIC database to conduct a retrospective analysis to investigate the first-time serum magnesium levels of 10,033 critically ill children admitted to the pediatric ICU, and analyzed association between serum magnesium and all-cause mortality. Smoothing spline plots, subgroup analysis and segmented multivariate logistic regression analysis were conducted to estimate the relative risk between serum magnesium and all-cause mortality. The shape of the curve was used to describe the relationship between magnesium and 28-day in-hospital mortality.

Results: There is a non-linear relationship between serum magnesium and 28-day in-hospital all-cause mortality. The U-type relationship between serum magnesium and all-cause mortality was observed. The optimal range of serum magnesium with the lowest risk of mortality was 0.74–0.93 mmol/L. As the serum magnesium level reaches the turning point (0.74 mmol/L), the risk of death decreases by 60% for every 0.1 mmol/L increase in serum magnesium; when the serum magnesium level exceeds 0.93, an increase of 0.1 mmol/L increases the risk of death by 38 %.

Conclusion: Serum magnesium has a U-shaped relationship with 28-day in-hospital all-cause mortality. Both low and high serum magnesium can increase the risk of death. The best serum magnesium range when the risk of death is the lowest is 0.74–0.93 mmol/L.

Keywords: magnesium, mortality, ICU, pediatric, safe medication

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INTRODUCTION

Magnesium is the fourth most plentiful mineral in the body and the second most plentiful intracellular cation (1). Sixty-seven percentage of magnesium is found in bone, 31% in cells and 1–2% in extra cellular fluids (2). Magnesium is a key electrolyte for maintaining cell membrane potential, a key co-factor for adenylate cyclase and sodium-potassium-adenine triphosphatase, an essential mineral for hundreds of enzymatic reactions

(3), and is involved in more than 300 biochemical reactions in the body with a range of important physiological roles (4). Magnesium plays an important role in electrolyte homeostasis, cell membrane stability and blood pressure regulation (5), energy production, storage and utilization, protein metabolism, inflammation (6), promotion of nerve conduction, insulin metabolism, myocardial contraction, regulation of vascular tone, atherosclerosis and thrombosis, proliferation and migration of vascular smooth muscle cells and endothelial cells, and vascular calcification (7).

To date, there is disagreement about the exact nature of magnesium and ICU mortality. Previous clinical studies have focused on mortality and hypomagnesemia, with the majority of studies focusing on a single type of magnesium abnormal status. Some studies have proposed low magnesium (8–10) or high magnesium status (11–13) as risk factors for mortality in ICU patients, while others have shown no association between low magnesium (14–17) and prognosis in ICU patients, and although hypomagnesemia is associated with mortality, it only occurs after ICU admission (14).

Previous studies only focused on adults. To my knowledge, only one study has investigated hypomagnesemia in pediatric ICU patients (18), but there are no studies on the relationship between serum magnesium levels and prognosis in pediatric ICU patients. In this study, we will investigate the serum magnesium levels of pediatric patients at the time of admission to the ICU, and we aim to assess the relationship between serum magnesium and 28-day in-hospital all-cause mortality in pediatric ICU patients.

METHODS

Subjects

We performed a retrospective analysis using the Pediatric Specialty Intensive Care (PIC) database, selecting 10,033 critically ill children with comprehensive laboratory test results. PIC (Pediatric Intensive Care) is a large pediatric-specific, single-center, bilingual database containing information related to children in the ICU at the Children's Hospital of ZheJiang University School of Medicine, China, from 2010 to 2018. The PIC database includes vital sign measurements, medications, laboratory measurements, fluid balance, diagnosis codes, length of stay, survival data, and more (19). The laboratory indicators we included are the results of the first inspection after admission to the ICU. Inclusion criteria: The results of magnesium are not missing. Exclusion criteria: Outliers (<1% or >99%) for magnesium results. The range of serum magnesium is between 0.59 and 1.58 mmol/L. ICU category including neonatal intensive care unit (NICU), surgery intensive care unit (SICU), pediatric Intensive Care Unit (PICU), cardiac intensive care unit (CICU). Vasoactive drugs including dopamine hydrochloride injection, dobutamine hydrochloride injection, adrenaline hydrochlaride injection, isoprenaline hydrochloride injection, phcnylephrine hydrochloride injection, norepinephrine bitartrate injection. Magnesium supplement drugs include: 25% magnesium sulfate injection, magnesium sulfate powder, hydrotalcite tablets, potassium aspartate and magnesium aspartate injection.

PIC database is a public database, this project was approved by the Institutional Review Board/Ethical Committee of the Children's Hosptial, Zhejiang University School of Medicine (2019_IRB_052). The requirement for individual patient consent was waived because the project did not impact clinical care, and all protected health information was deidentifie (19). We formally applied for access through the procedures recorded on the PIC website and PhysioNet, and we have signed a data usage agreement. We handle data responsibly and adhere to the principle of cooperative research.

Statistical Analysis

Data is expressed as mean (SD) or median (Q1-Q3) for continuous variables and percentage (%) for dichotomous variables. A smooth curve fit plot of serum magnesium was created to examine the shape of the relationship between serum magnesium and 28-day in-hospital all-cause mortality. We applied a two-segment linear regression model to test the threshold effect of serum magnesium on mortality based on smoothing plots. A segmented regression model was then used to compare the differences between models I and II by performing log-likelihood ratio tests for the single-linear linear regression model and the two-segment linear model. $p < 0.05$ means Model II is significantly different from Model I, which indicates a non-linear relationship.

An additional turning point for serum magnesium was determined by curve fitting the mortality corresponding to the turning point in the graph, and the range between the two points was considered to be the threshold for low risk of death.

Logistic regression models were used to examine the effect of serum magnesium and other variables on the occurrence of 28-day in-hospital all-cause mortality. Because of the small variation in serum magnesium in the human body, the risk associated with 28-day in-hospital all-cause mortality is reported per 0.1 mmol/L of continuous serum magnesium. Data was analyzed with the use of the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3). All *P*-values for statistics were two-tailed, and $P < 0.05$ was regarded as statistically significant.

RESULTS

Baseline Characteristics and Laboratory Test Results

Figure 1 is flowchart of participants. Our study included 10,033 children, including 5,677 boys and 4,356 girls. Median age at ICU admission was 8.68 months (Q1-Q3: 1.22–40.21), median length of stay in ICU was 1.98 (0.90–7.76) days, median length of stay in hospital was 13.60 (8.02–22.03) days, in-hospital all-cause mortality is 3.83% (384 patients), 28-day in-hospital all-cause mortality is 3.24% (325 patients). The median serum magnesium concentration is 0.87 (0.81–0.94) mmol/L.

Tables 1, **2** describe the baseline characteristics of the subjects, including demographic characteristics and some laboratory test results that may be related to the occurrence of mortality.

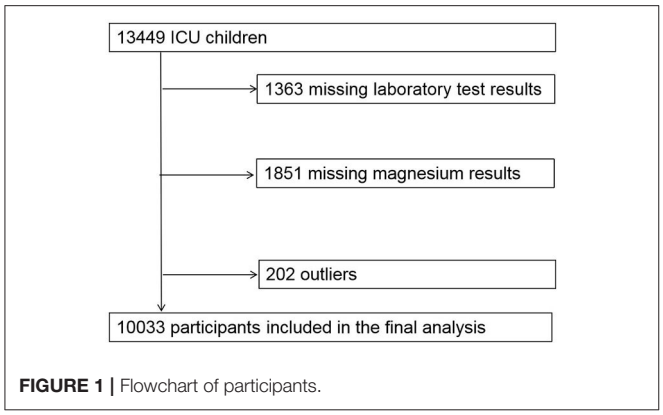

FIGURE 1 | Flowchart of participants.

TABLE 1 | Baseline characteristics of the study participants.

	28-day in-hospital mortality = 0	28-day in-hospital mortality = 1	*p*-value
No. of participants	9,708	325	
Age (months) Median (Q1-Q3)	8.91 (1.32–41.09)	1.78 (0.10–19.00)	<0.001
Vasoactive drugs			0.518
0	7,380 (76.02%)	242 (74.46%)	
1	2,328 (23.98%)	83 (25.54%)	
ICU category, *N* (%)			<0.001
NICU	2,391 (24.63%)	130 (40.00%)	
SICU	2,381 (24.53%)	31 (9.54%)	
CICU	2,413 (24.86%)	38 (11.69%)	
PICU	1,399 (14.41%)	98 (30.15%)	
General ICU	1,124 (11.58%)	28 (8.62%)	
Gender, *N* (%)			0.052
Male	5,476 (56.41%)	201 (61.85%)	
Female	4,232 (43.59%)	124 (38.15%)	
Magnesium supplement, *N* (%)			0.104
0	9,035 (93.07%)	310 (95.38%)	
1	673 (6.93%)	15 (4.62%)	
Prematurity			0.063
0	9,032 (93.04%)	311 (95.69%)	
1	676 (6.96%)	14 (4.31%)	
Length of ICU stay, median (Q1-Q3)	1.96 (0.90–7.68)	3.95 (1.11–8.91)	0.002
Length of hospital stay, median (Q1-Q3)	13.81 (8.10–22.61)	5.14 (1.74–11.84)	<0.001

TABLE 2 | Characteristics of clinical laboratory results of study participants.

	28-day in-hospital mortality = 0	28-day in-hospital mortality = 1	*p*-value
No. of participants	9,708	325	
Magnesium (mmol/L)	0.89 ± 0.13	0.95 ± 0.20	<0.001
Albumin (g/L)	39.55 ± 6.77	33.60 ± 8.27	<0.001
Hemoglobin (g/L)	124.24 ± 29.22	125.15 ± 38.99	0.591
Tcho (mmol/L)	3.38 ± 1.28	2.61 ± 1.63	<0.001
ALT (U/L), Median (Q1-Q3)	17.00 (11.00–29.00)	24.00 (14.00–75.00)	<0.001
Creatinine (μmol/L)	72.42 ± 358.56	78.25 ± 62.52	<0.001
Calcium (mmol/L)	2.31 ± 0.24	2.14 ± 0.30	<0.001
Phosphate (mmol/L)	1.86 ± 0.65	2.18 ± 1.03	<0.001
Neutrophils (×10^9/L)	5.63 ± 5.28	8.35 ± 6.96	<0.001
Lactate (mmol/L)	2.38 ± 2.02	5.61 ± 5.34	<0.001
Blood culture results			0.001
0	8,960 (92.30%)	284 (87.38%)	
1	748 (7.70%)	41 (12.62%)	

TABLE 3 | Threshold effect analysis for the relationship between magnesium (per 0.1 mmol/L) and 28-day in-hospital all-cause mortality.

Models	Risk of mortality adjusted OR (95%CI)	*P*-value
Model I		
One line slope	1.30 (1.19, 1.42)	<0.0001
Model II		
Turning point (K)	7.4	
< 7.4 slope 1	0.41 (0.24, 0.70)	0.0011
> 7.4 slope 2	1.39 (1.27, 1.52)	<0.0001
Slope 2–Slope 1	3.39 (1.92, 5.98)	<0.0001
Predicted at 7.4	−4.20 (−4.39, −4.00)	
LRT test	<0.001	

Data were presented as OR (95%CI) P-value; Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test ($p < 0.05$ means Model II is significantly different from Model I, which indicates a non-linear relationship); adjust for gender, vasoactive drugs, age, ICU category, magnesium supplement, albumin; hemoglobin; ALT; Creatinine; absolute neutrophil; lactate; Tcho, Calcium, phosphorus, prematurity, blood culture results, length of ICU stay. $p < 0.05$ indicates that Model II is significant different from Model I.

Threshold Effect of Magnesium and 28-Day Mortality

The results in **Table 3** show that the turning point value (0.74 mmol/L) of magnesium was found through the piece-wise regression model between magnesium and the risk of 28-day in-hospital all-cause mortality. An additional turning point for serum magnesium was determined by curve fitting the mortality corresponding to the turning point in the graph, and the range between the two points (0.74–0.93 mmol/L) was considered to be the threshold for low risk of death.

The risk of 28-day in-hospital mortality decreased by 59% in patients per 0.1 mmmol/L unit increase of magnesium when magnesium ranged from 0.59 to 0.74 mmol/L and increased by 39% in patients per 0.1 mmmol/L unit increase of magnesium when magnesium ranged from 0.93 to 1.58 mmol/L (log-likelihood ratio test: $P < 0.001$, it demonstrated a non-linear

relationship between magnesium and risk of 28-day in-hospital all-cause mortality).

Figure 2 shows a smoothed spline plot of serum magnesium and risk of 28-day in-hospital all-cause mortality. The relationship between serum magnesium and 28-day in-hospital all-cause mortality was U-shaped, with a significant decrease in the incidence of 28-day in-hospital all-cause mortality with increasing serum magnesium concentrations at <0.74 mmol/L. At >0.93 mmol/L, the incidence of 28-day in-hospital all-cause mortality increased significantly with increasing serum magnesium concentrations.

Figure 3 shows a smooth spline plot after stratification according to the use of magnesium supplements or not. In patients without magnesium supplementation, the relationship between serum magnesium and 28-day in-hospital all-cause mortality remained U-shaped. In patients using magnesium supplementation, there was no difference in mortality change with increasing serum magnesium concentrations at <0.74 mmol/L. At >0.93 mmol/L, mortality increased significantly with increasing serum magnesium concentrations.

Subsection Regression Analysis of Magnesium and 28-Day Mortality

Table 4 shows the results of the multiple regression of the effect of serum magnesium on 28-day in-hospital all-cause mortality. Multivariate regression models included other variables, including sex, age in months, ICU category, vasoactive drugs, magnesium supplementation, albumin; hemoglobin; alanine aminotransfease (ALT); Creatinine; absolute neutrophil; lactate; total cholesterol (Tcho), Calcium, phosphorus, prematurity, blood culture results, length of ICU stay. Serum magnesium of 0.74 and 0.93 mmol/L were used as the cut-off point. When serum magnesium was <0.74 mmol/L, serum magnesium was a protective factor for 28-day in-hospital all-cause mortality. After full adjustment for con-founders, the risk of 28-day in-hospital all-cause mortality was reduced by 59% for each 0.1 mmol/L increase in serum magnesium. When serum magnesium was >0.93 mmol/L, serum magnesium was a risk factor for 28-day in-hospital all-cause mortality. After full adjustment for con-founders, the risk of 28-day in-hospital all-cause mortality increased by 37% for each 0.1 mmol/L increase in serum magnesium.

DISCUSSION

Electrolyte abnormalities are common armong patients in the ICU (20). No comprehensive and uniform understanding of the relationship between serum magnesium and mortality. Our study found a U-shaped relationship between serum magnesium and 28-day in-hospital mortality in the pediatric

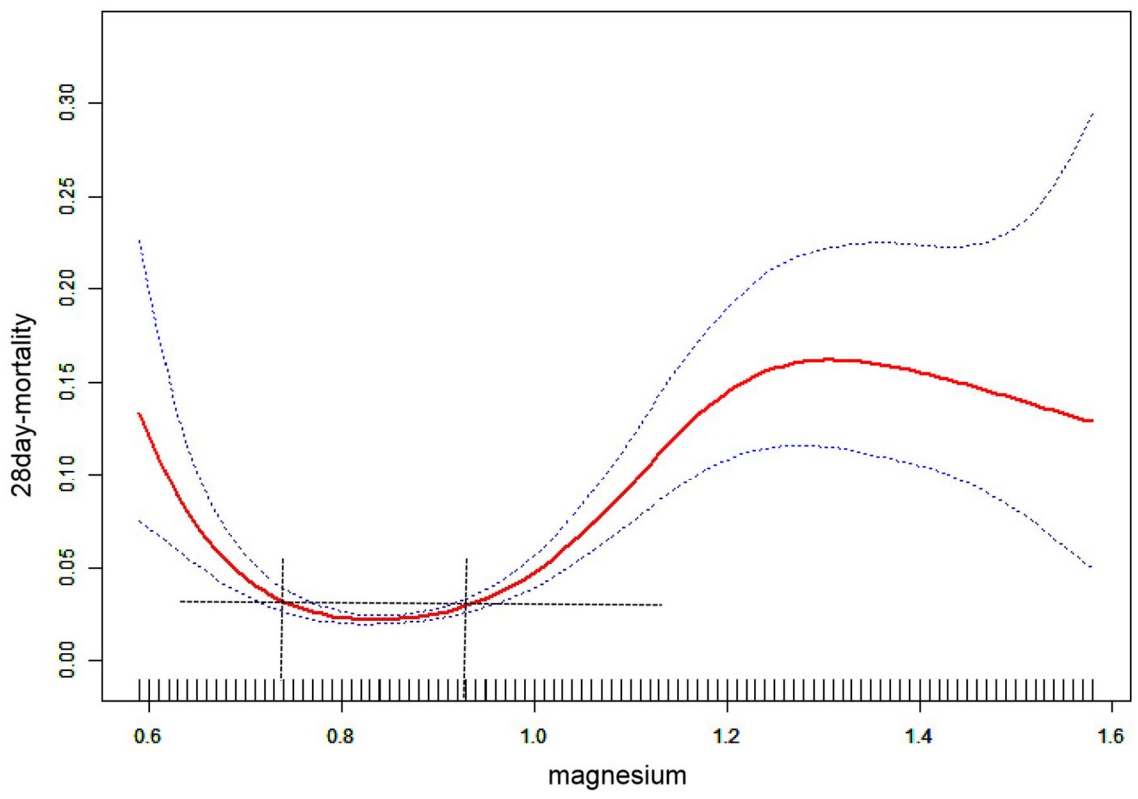

FIGURE 2 | The association between magnesium and 28-day in-hospital all-cause mortality. The red line represents the fitted curve of magnesium and 28-day mortality, and the blue line represents the 95% confidence interval of the curve.

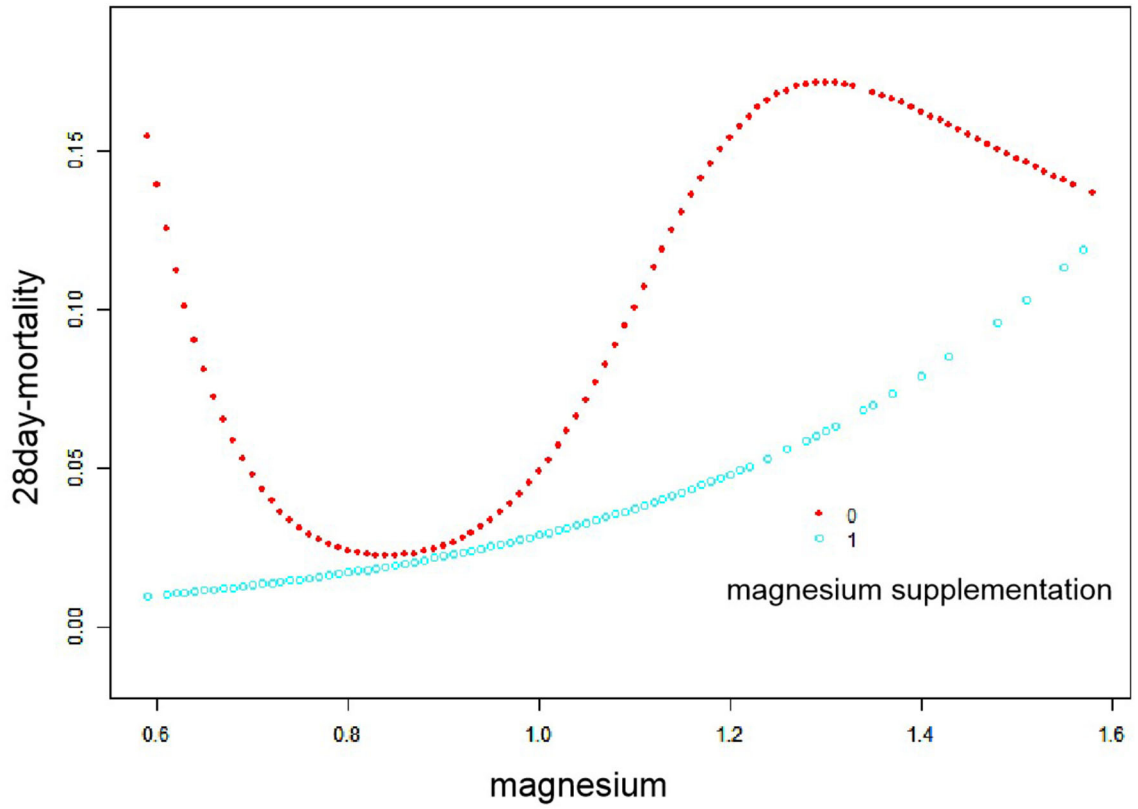

FIGURE 3 | Smooth fitting curve stratified by magnesium supplementation. Red dots represent children who are not taking magnesium supplements, and blue dots represent children who are taking magnesium supplements.

TABLE 4 | Individual effect of magnesium on 28-day in-hospital all-cause mortality using piece-wise linear regression.

Exposure	*n*	Non-adjusted		Adjust model I		Adjust model II	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Magnesium: [0.59–0.74] mmol/L							
Per 0.1 mmol/L	858	0.29 (0.14, 0.59)	0.0006	0.29 (0.14, 0.60)	0.0008	0.41 (0.17, 0.96)	0.0410
Magnesium: (0.93–1.58] mmol/L							
Per 0.1 mmol/L	2,717	1.38 (1.26, 1.52)	<0.0001	1.36 (1.23, 1.50)	<0.0001	1.37 (1.19, 1.57)	<0.0001

Adjust model I: Adjusted for gender, age, ICU category.
Adjust model II: adjust for gender, vasoactive drugs, age, ICU category, magnesium supplement, albumin; hemoglobin; ALT; Creatinine; absolute neutrophil; lactate; Tcho, Calcium, phosphorus, prematurity, blood culture results, length of ICU stay.

ICU. There is a non-linear relationship between serum magnesium and mortality, and the threshold effect of serum magnesium on mortality is significant. Before the turning point (0.74 mmol/L), the mortality rate decreased with the increase of serum magnesium level; after the turning point (0.93 mmol/L), the mortality rate increased with the increase of serum magnesium level. To my knowledge, we reveal for the first time a U-shaped relationship between serum magnesium and 28-day in-hospital mortality, presenting strong evidence for a safe range of serum magnesium in magnesium replacement therapy for pediatric ICU patients.

Magnesium deficiency usually occurs in critical illness and is associated with higher mortality and poorer clinical outcomes in the ICU (8–10). The literature reports that hypomagnesemia occurs in 40% of hospitalized patients, ∼60% of postoperative patients, 65% of medical ICU patients, and up to 90% of surgical ICU patients (20). Although the vast majority of studies concluded that hypomagnesemia is a risk factor for poor prognosis, there are still several publications reporting no association between hypomagnesemia and prognosis of ICU patients (14–17). Our findings show that in the pediatric ICU, hypomagnesemic status leads to increased mortality when serum magnesium is <0.74 mmol/L and that magnesium

supplementation reduces 28-day in-hospital all-cause mortality when patients are first admittion to the ICU unit with serum magnesium <0.74 mmol/L.

Magnesium is an essential co-factor in hundreds of enzyme systems (8). The effects of magnesium on these enzymes, as well as on other important biological processes such as glycolysis, oxidative phosphorylation, nucleotide metabolism, protein biosynthesis, and phosphatidylinositol turnover, emphasize the importance of magnesium in cellular metabolism. Lower magnesium levels are associated with increased interleukin-1, tumor necrosis factor-α, and interferon-γ, are associated with chronic inflammatory stress, and have an impact on mortality (20–23). Magnesium ions regulate intracellular calcium levels, which in turn affect smooth muscle tone. By regulating smooth muscle tone, magnesium deficiency is thought to lead to hypertension, neuromuscular hyperexcitability, bronchial airway constriction, coronary vasospasm, seizures and increased mortality. Disturbed magnesium levels measured in critically ill patients are more common than any other electrolyte (24). However, excessive serum magnesium can cause damage to cardiac systole and diastole, can impair acetylcholine release and reduce muscle sensitivity to acetylcholine. High serum magnesium may lead to severe arrhythmias, myocardial depression, and vasodilation, which can lead to hypotension (25).

There are also conflicting views on the clinical effects of magnesium supplementation. Some studies have proposed that low dietary magnesium intake increases the risk of cardiovascular disease and that magnesium supplementation is beneficial in the treatment of acute myocardial infarction (25). Magnesium supplementation improved blood pressure control (26), insulin sensitivity (27), and endothelial function (28). Magnesium has a protective effect against endothelial cell injury and oxidative stress (29). Prophylactic intravenous magnesium reduces the incidence of postoperative arrhythmias in pediatric patients. Numerous studies have been conducted to address the negative effects of the high prevalence of hypomagnesemia in ICU patients, such as increased mortality, the need for prolonged mechanical ventilation (MV), and increased length of stay in the ICU. The effectiveness of magnesium replacement therapy has been evaluated in several large clinical studies for myocardial infarction, but their results have been inconsistent (30). Similarly studies have concluded that even with the negative effects of hypomagnesemia, there is insufficient evidence for the benefit of magnesium replacement therapy in ICU patients with hypomagnesemia (31). Another study looked at the use of intraoperative magnesium in congenital heart disease in relation to reducing the odds of all postoperative arrhythmias. The results stated that there was no evidence that greater doses of magnesium were associated with a greater reduction in arrhythmia risk, and there was little evidence of a dose-response effect (32). Across the United States, there has been a significant increase in the use of intravenous magnesium for the treatment of children with worsening asthma. However, magnesium replacement therapy has not been associated with changes in hospitalization rates, ICU admissions, or 7-day all-cause readmission rates (33).

With the increased emphasis on avoiding or treating hypomagnesemia, clinicians may not be aware of the potential harm associated with hypomagnesemia, such as hypotension, prolonged QRS time frame, respiratory failure, and even cardiac arrest (24). For example, in a large study of more than 10,000 ICU patients, hypomagnesemia was associated with lower systolic blood pressure and also increased the likelihood of requiring blood pressure-independent vasopressant therapy (34). In a cross-sectional online survey of two national associations of pediatric emergency physicians in Canada and the United States, 24% of respondents taking magnesium had experienced associated severe hypotension requiring treatment and 2% had experienced apnea-related symptoms (35).

In fact, a growing number of clinical studies question the benefits of magnesium supplementation and the safe range of serum magnesium in patients with acute myocardial infarction. A study suggested that the optimal magnesium range for patients with acute myocardial infarction should be lower than the range recommended by current acute myocardial infarction guidelines (36). In addition, the ISIS-4 trial (Fourth International Infarct Survival Study) included 58,050 patients with suspected acute myocardial infarction, but magnesium supplementation did not show a positive effect (37).

Our findings could well explain the above inconsistency regarding the clinical efficacy of magnesium supplementation. It is because of the unique U-shaped relationship between serum magnesium and mortality that simple thinking should not be used to avoid low or high magnesium, but rather to introduce the concept of an optimal magnesium concentration range, which we found to be around 0.74–0.93 mmol/L in pediatric ICU patients, and clinical magnesium supplementation should be done with caution and care and not overkill.

The serum magnesium level is kept constant within very narrow limits. Regulation takes place mainly *via* kidneys. The Mayo Clinic recommends the following serum magnesium reference ranges: 0–2 years: 0.67–1.125 mmol, 3–5 years: 0.67–1.08 mmolL, 6–8 years: 0.67–1.04 mmol, 9–11 years: 0.67–1 mmol, 12–17 years: 0.67–0.96 mmol, >17 years: 0.71–0.96 mmol. In China, the recommended reference range for serum magnesium in the National Clinical Laboratory Procedure is 0.75–1.02 mmol/L for adults and 0.5–0.9 mmol/L for children. One millimoles per litre = 2.4 mg/dl. Due to the influence of age on the concentration of serum magnesium, we adjusted for age as a confounding factor.

One study reported pediatric serum magnesium concentration reference intervals are about 0.55–1.03 mmol/L (38). This reference range is closest to the serum magnesium reference range for Chinese children. However, the normal range suggested in another study for preterm and full-term infants in the first 2 weeks of life was taken as 0.7–1.5 mmol/L (39). In our present study, the median serum magnesium concentration is 0.87 mmol/L, the 25th percentile is 0.81 mmol/L and the 75th percentile is 0.94 mmol/L. The turning point for the threshold effect of serum magnesium on 28-day in-hospital all-cause mortality in the pediatric ICU was 0.74–0.93 mmol/L.

There are some shortcomings in our study; firstly, *in vivo*, magnesium is found almost exclusively in cells. Serum contains only 0.3% of total body magnesium, and total serum magnesium concentrations do not adequately reflect the body's magnesium

stores. Because magnesium is a tightly controlled element, serum levels may not reflect magnesium deficiency until the body is severely depleted of magnesium. Magnesium tolerance tests and ionized magnesium ions are alternative laboratory assessment methods; however, each has its own difficulties in the ICU setting (9). Next, this study was a single-center retrospective study, and although every effort was made to adjust for potential confounding factors through multifactorial logistic analysis, there are still other inpatient variables that may confound the predictive effect of serum magnesium, e.g., mechanical ventilation.

CONCLUSION

The first determination of serum magnesium in critically ill children in China's ICU has a U-shaped relationship with 28-day in-hospital all-cause mortality. Both low and high serum magnesium can increase the risk of death. The best serum magnesium value when the risk of death is the lowest is 0.74–0.93 mmol/L. In the present study, we present the importance of serum magnesium management in pediatric ICU patients. Future 28-day in-hospital all-cause mortality in pediatric ICU patients could potentially be reduced by aggressive interventions for abnormal magnesium concentrations. Our current work provides data suggesting that serum magnesium levels not only provide important prognostic information about pediatric ICU patients, but that targeting optimal serum magnesium levels may be a promising therapeutic target for magnesium replacement therapy.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: http://pic.nbscn.org//.

AUTHOR CONTRIBUTIONS

CY analyzed the data, drafted the manuscript, contributed to study design, and revised the article. CZ contributed to data collation. ZH and CY made contribution to the conception, design, and revision of the revised manuscript. All authors have read and approved the final manuscript.

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Impact of Overhydration on Left Ventricular Hypertrophy in Patients With Chronic Kidney Disease

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Objective: Volume overload is a frequent feature related to left ventricular hypertrophy (LVH) in dialysis patients, but its influence on patients with chronic kidney disease (CKD) not on dialysis has not been accurately uncovered. This article was to examine the relationship between overhydration (OH) and LVH in patients with CKD not yet on dialysis.

Methods: A total of 302 patients with CKD stages 1–4 were included. Participants were divided into different subgroups according to occurring LVH or not, and OH tertiles. Clinical and laboratory parameters were compared among groups. Spearman correlation analyses were adopted to explore the relationships of echocardiographic findings with the clinical and laboratory characteristics. Binary logistic regression models were performed to estimate the odds ratios (ORs) for the associations between OH and LVH. Restricted cubic splines were implemented to assess the possible non-linear relationship between OH and LVH. LVH was defined as left ventricular mass index (LVMI) >115 g/m^2 in men and >95 g/m^2 in women.

Results: Of the enrolled patients with CKD, the mean age was 45.03 $\pm$ 15.14 years old, 165 (54.6%) cases were men, and 65 (21.5%) cases had LVH. Spearman correlation analyses revealed that OH was positively correlated with LVMI ($r = 0.263$, $P < 0.001$). After adjustment for age, gender, diabetes, body mass index (BMI), systolic blood pressure (SBP), hemoglobin, serum albumin, estimated glomerular filtration rate (eGFR), and logarithmic transformation of urinary sodium and urinary protein, multivariate logistic regression analyses demonstrated that both the middle and highest tertile of OH was associated with increased odds of LVH [OR: 3.082 (1.170–8.114), $P = 0.023$; OR: 4.481 (1.332–15.078), $P = 0.015$, respectively], in comparison to the lowest tierce. Restricted cubic spline analyses were employed to investigate the relationship between OH and LVH, which unfolded a significant non-linear association (P for non-linear $= 0.0363$).

Furthermore, patients were divided into two groups according to CKD stages. The multivariate logistic regression analyses uncovered that increased odds of LVH were observed in the middle and the highest tertile of OH [OR: 3.908 (0.975–15.670), $P = 0.054$; OR: 6.347 (1.257–32.054), $P = 0.025$, respectively] in patients with stages 1–2.

Conclusion: These findings suggest that a higher level of OH was associated with a higher occurrence of LVH in patients with CKD not on dialysis, especially in patients with CKD stages 1–2.

Keywords: overhydration, left ventricular mass index, left ventricular hypertrophy, chronic kidney disease, odds ratio

INTRODUCTION

As chronic kidney disease (CKD) progresses, the prevalence of cardiovascular disease (CVD) and cardiac death is strikingly rising (1). Increasing evidence has revealed that CVD instead of end-stage renal disease (ESRD) is a real burden in patients with mild-to-moderate renal injury (2–4). Of all the cardiac problems in patients with CKD, left ventricular hypertrophy (LVH), histologically characterized by myocardial fibrosis, is the most common structural impairment (5). LVH not only accelerates renal dysfunction but also elevates the proportion of sudden cardiac death in patients with CKD (6–8). For decades, approaches to predict LVH have been constantly studied and mostly rely upon the clinical factors containing blood pressure, BMI, estimated glomerular filtration rate, serum phosphate, and fibroblast growth factor 23 (9–13). However, it is indispensable to discover novel predictors for LVH in patients with CKD, which is beneficial to more effective therapeutic interventions.

Volume expansion is a common complication of CKD (14) and is frequently related to inflammation, CKD progression, and mortality (15–17). Therefore, exact assessment and management of fluid status are of paramount importance in these patients. In comparison with conventional tools to evaluate fluid volume, bioelectrical impedance analysis (BIA) has been a simple, non-invasive, and high-efficient means, and is widely used in patients with CKD (18). Until recently, overhydration (OH), generated from a three-compartment model, has replaced the ratios of extracellular water (ECW)/total body water (TBW) and ECW/intracellular water (ICW) as the representative of evaluating volume status (19). Previous studies have reported the predictive impacts of OH on LVH in patients with CKD stage 5 (20, 21). However, it has not been adequately illustrated about these parameters in patients with an estimated glomerular filtration rate (eGFR) of more than 15 ml/min/1.73 m^2. With this aim in mind, this study investigated the association of OH with clinical features and LVH in patients with CKD not yet on dialysis.

MATERIALS AND METHODS

Subjects

A total of 386 patients with CKD with stages 1–4 from December 2019 to January 2021 were retrospectively reviewed and they were treated at the department of nephrology, the First Affiliated Hospital of Nanjing Medical University. The inclusion criteria were patients diagnosed with CKD, whose eGFR >15 ml/min/1.73 m^2. CKD is defined as abnormalities of kidney structure or function, present for >3 months in accordance with the guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice (22). Exclusion criteria were as follows: (1) lack of body composition index and echocardiography information; (2) implantation of a cardiac pacemaker, defibrillator, or metallic objects; (3) the amputation of any extremity; (4) clinical state affecting body composition, such as liver cirrhosis, active infectious disease or acute cardiovascular events within 3 months before screening for inclusion; (5) left ventricular ejection fraction (LVEF) < 50%; (6) comorbid cardiovascular disease, such as coronary artery disease, atrial fibrillation, valvular heart disease or primary cardiomyopathy; (7) pregnancy and malignancy. Ultimately, 302 participants were included (**Figure 1**).

Clinical and Laboratory Measurements

The patient's clinical characteristics containing age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), history of hypertension and diabetes, and current medication were recorded at the enrollment. The plasma levels of creatinine, albumin, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hemoglobin, and C-reactive protein (CRP) were measured using blood samples taken from patients who were under fasting condition. In order to assess urinary protein, sodium, and potassium, patients were required to simultaneously gather 24-h urine specimens. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)^{2009} equation (23).

Body Composition Measurements

Assessment of volume status was performed on a body composition monitor (BCM) (Fresenius Medical Care, Bad Homburg, Germany) by the same experienced nurse according to the instrument instructions. The patient's clinical parameters containing age, gender, height, and weight were inputted into the device. Electrodes were placed on the hand and foot of patients' non-dominant side, and then electrical responses were collected every 50 discrete frequencies from 5 to 1,000 kHZ. Given the measured impedance information, TBW, ECW, and intracellular

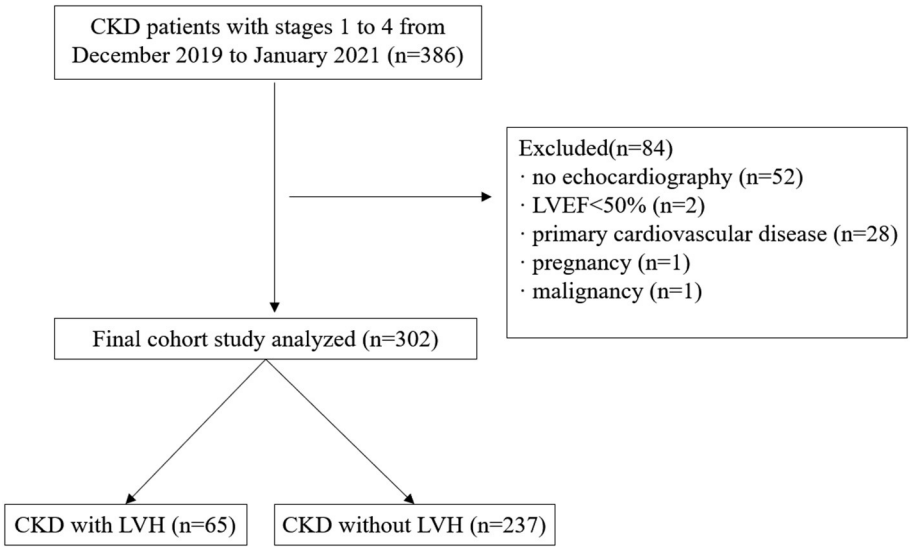

FIGURE 1 | Flowchart of study participants. CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

water (ICW) were calculated by the equations proposed by Moissl et al. (24). Over the next few years, Chamney et al. (19) proposed a three-compartment model to describe OH in absolute liters. The model consists of lean tissue mass, adipose tissue mass, and OH. OH is calculated by subtracting water in the tissue measured by physiologic models under normal status from ECW present in tissue that was actually measured. Fluid overload (FO) was defined as an absolute OH $\geq$1.1 L in this study (14).

Echocardiographic Measurements

Echocardiography was performed using an ultrasound machine (Vivid E9; GE Vingemed Ultrasound AS, Horten, Norway) with a 2.5-MHz transducer by a single experienced cardiologist who was completely blinded to the patient information. M-mode and two-dimensional measurements were used to perform cardiac chamber quantification in accordance with the guidelines of the American Society of Echocardiography (25). Thereafter, the dimensions of the interventricular septal thickness (IVST), left ventricular end-diastolic dimension (LVDd), left ventricular posterior wall thickness (PWT), left atrial dimension (LAD), and LVEF using the biplane Simpson's method were measured. IVST and PWT were measured at end-diastole. At the level of the mitral valve tips during diastole, pulse-wave Doppler was employed to observe transmitral early diastolic velocity (E), peak velocity flow in the late diastole caused by atrial contraction (A), and their deceleration time in the apical four-chamber view. Meanwhile, early diastolic mitral annular tissue velocity (e'), the average of septal and lateral mitral annular velocities, was calculated as well as E/e'. The following equations were performed according to the American Society of Echocardiography guidelines (25). Left ventricular mass $= 0.8 \times 1.04 \times [(\text{IVST} + \text{LVDd} + \text{PWT})^3 - \text{LVDd}^3] + 0.6$ (g). Body surface area (BSA) $= (0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725})$ m^2. Left ventricular mass index (LVMI) = LVM/BSA (g/m^2). Relative wall thickness (RWT) $= 2 \times$ PWT/LVDd. The left ventricular hypertrophy (LVH) was defined as an LVMI $>$ 115 g/m^2 in men and $>$ 95 g/m^2 in women (25).

Statistical Analysis

Participants were categorized into subgroups according to occurring LVH or not, and OH tertiles. Data were presented as mean $\pm$ SD, median, and interquartile range or percentage as appropriate. Comparisons between groups were performed using Student's *t*-test or ANOVA, Mann–Whitney test, Kruskal–Wallis test, or chi-squared test as appropriate. Spearman correlation analyses were adopted to explore the relationships of echocardiographic findings with clinical and laboratory parameters. The ORs for the associations between OH and LVH were evaluated by binary logistic regression models. Crucial covariates for LVH, including age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, eGFR, urinary sodium excretion, and urinary protein excretion, were selected based on prior knowledge and the findings of univariable analyses were adjusted in multivariable analyses. Possible non-linear relationships between OH and LVH were examined with restricted cubic splines using the same multivariable model (26). $P < 0.05$ was considered statistically significant. All the statistics were done in IBM SPSS version 20.0 and R version 4.1.0.

RESULTS

Baseline Clinical and Laboratory Characteristics of Patients With CKD

In total, 302 patients with CKD stages 1–4 were recruited in this study (**Table 1**). Their mean age was 45.03 $\pm$ 15.14 years old, and 54.6% of patients were men. Patients with CKD stages

TABLE 1 | Comparisons of clinical, laboratory, and echocardiographic parameters and volume status between the non-LVH and LVH groups in patients with CKD.

	Total (n = 302)	**Non-LVH (n = 237)**	**LVH (n = 65)**	***P*-value**
Age (years)	45.03 ± 15.14	42.69 ± 14.66	53.58 ± 13.83	**<0.001**
Sex (male/female)	165/137	140/97	25/40	**0.003**
BMI (kg/m^2)	24.61 ± 3.70	24.51 ± 3.74	24.97 ± 3.58	0.377
SBP (mmHg)	130.59 ± 18.24	127.98 ± 16.77	140.09 ± 20.27	**<0.001**
DBP (mmHg)	81.85 ± 12.47	81.25 ± 12.60	84.02 ± 11.85	0.114
MAP (mmHg)	98.09 ± 13.26	96.83 ± 13.11	102.71 ± 12.86	**0.001**
Hypertension (%)	140 (46.4)	92 (38.8)	48 (73.8)	**<0.001**
Diabetes (%)	51 (16.9)	29 (12.2)	22 (33.8)	**<0.001**
LAD (cm)	3.30 (3.00, 3.70)	3.20 (2.90, 3.50)	3.70 (3.20, 4.00)	**<0.001**
LVDd (cm)	4.60 (4.30, 4.90)	4.50 (4.20, 4.80)	4.90 (4.70, 5.10)	**<0.001**
LVMI (g/m^2)	87.91 (74.77, 99.79)	83.34 (71.49, 91.21)	113.43 (102.53, 127.88)	**<0.001**
RWT	0.42 (0.39, 0.44)	0.42 (0.38, 0.44)	0.43 (0.41, 0.46)	**0.004**
LVEF (%)	64.20 (62.40, 65.80)	64.40 (62.70, 65.90)	63.70 (61.80, 65.40)	**0.007**
E/e' ratio	7.05 (6.00, 9.10)	6.80 (5.80, 8.25)	9.50 (7.35, 11.55)	**<0.001**
E/A ratio	0.90 (0.70, 1.30)	1.00 (0.80, 1.30)	0.80 (0.70, 1.20)	**0.005**
eGFR (ml/min/1.73 m²)	92.95 (61.24, 111.97)	96.12 (69.84, 114.18)	77.98 (41.05, 103.25)	**0.001**
Scr (μmol/L)	79.15 (60.15, 112.95)	79.00 (60.35, 107.15)	83.10 (58.25, 134.50)	0.346
Serum albumin (g/L)	35.45 (26.40, 39.60)	36.50 (27.10, 39.90)	30.10 (25.35, 37.15)	**0.010**
TG (mmol/L)	1.59 (1.09, 2.30)	1.57 (1.08, 2.31)	1.66 (1.14, 2.31)	0.482
TC (mmol/L)	5.10 (4.20, 6.26)	4.99 (4.20, 6.10)	5.23 (4.28, 6.63)	0.362
LDL-C (mmol/L)	3.03 (2.42, 3.77)	2.96 (2.43, 3.77)	3.18 (2.40, 3.93)	0.557
HDL-C (mmol/L)	1.14 (0.96, 1.38)	1.14 (0.96, 1.40)	1.14 (0.94, 1.35)	0.659
Hemoglobin (g/L)	128.43 ± 21.78	131.77 ± 20.92	116.28 ± 20.64	**<0.001**
CRP (mg/L)	1.87 (1.25, 3.18)	1.80 (1.23, 3.04)	2.00 (1.52, 3.62)	0.073
Urinary protein (g/d)	1.14 (0.38, 3.91)	0.92 (0.34, 3.01)	2.27 (0.86, 5.65)	**0.001**
Urinary sodium (mmol/d)	125.75 (86.85, 166.38)	120.60 (86.30, 166.65)	136.20 (89.55, 167.65)	0.324
Urinary potassium (mmol/d)	30.20 (23.15, 38.20)	30.30 (22.90, 38.00)	29.60 (23.60, 38.50)	0.758
OH (L)	0.50 (-0.50, 1.93)	0.20 (-0.65, 1.55)	1.30 (0.25, 3.60)	**<0.001**
ECW (L)	15.55 (13.30, 18.70)	15.50 (13.30, 18.50)	15.90 (13.45, 19.65)	0.422
ICW (L)	19.20 (16.00, 22.65)	19.70 (16.35, 22.95)	17.40 (14.95, 20.65)	**0.005**
TBW (L)	34.90 (29.40, 41.70)	35.30 (29.50, 41.90)	34.00 (28.20, 40.20)	0.244
FO (%)	110 (36.4)	74 (31.2)	36 (55.4)	**<0.001**
ACEI/ARB (%)	125 (41.4)	94 (39.7)	31 (47.7)	0.244
CCB (%)	94 (31.1)	57 (24.1)	37 (56.9)	**<0.001**
β-blocker (%)	25 (8.3)	14 (5.9)	11 (16.9)	**0.004**
Diuretic (%)	21 (7.0)	17 (7.2)	4 (6.2)	0.991

CKD, chronic kidney disease; LVH, left ventricular hypertrophy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; CRP c,-reactive protein; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; OH, overhydration; ECW, extracellular water; ICW, intracellular water; TBW, total body water; FO fluid overload; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; CCB, calcium-channel blocker.

Data were presented as the mean ± SD, the median with interquartile range or counts, and percentages. A two-tailed $p < 0.05$ was considered statistically significant. The bold values mean that $P < 0.05$.

1, 2, 3, and 4 accounted for 53.0, 22.8, 17.9, and 6.3% of the enrolled patients, respectively. LVH was present in 21.5% of all the enrolled patients. Suffering from LVH was 40 (17.5%) cases in CKD stages 1–2 but 25 (34.2%) cases in CKD stages 3–4. There was a significant increase in the prevalence of LVH in patients with CKD 3–4 as opposed to CKD 1–2 ($P = 0.002$). A total of 140 (46.4%) cases had hypertension, and 51 (16.9%) cases had diabetes. Among all the enrolled participants, the median OH, LVMI, urinary protein excretion, and eGFR were 0.50 L [interquartile range (IQR) −0.50–1.93], 87.91 g/m^2 (IQR 74.77–99.79), 1.14 g/d (IQR 0.38–3.91), and 92.95 ml/min/1.73 m² (IQR 61.24–111.97), respectively. Next, patients were categorized into two groups according to the occurrence of LVH. Compared with the patients without LVH, significantly higher levels of

TABLE 2 | Comparisons of clinical, laboratory, and echocardiographic parameters and volume status according to OH tertiles in patients with CKD.

Parameter	OH (L)			*P*-value
	Tertile 1 (≤−0.1)	**Tertile 2 (−0.1–1.2)**	**Tertile 3 (>1.2)**	
n	105	99	98	
Age (years)	40.72 ± 12.87	44.33 ± 14.83	50.36 ± 16.20	**<0.001**
Sex (male/female)	57/48	45/54	63/35	**0.029**
BMI (kg/m^2)	24.65 ± 3.99	24.36 ± 3.51	24.81 ± 3.60	0.693
SBP (mmHg)	124.81 ± 16.14	129.98 ± 16.06	137.39 ± 20.23	**<0.001**
DBP (mmHg)	80.10 ± 13.32	82.18 ± 12.02	83.38 ± 11.87	0.166
MAP (mmHg)	95.01 ± 13.44	98.11 ± 12.48	101.38 ± 13.15	**0.003**
Hypertension (%)	43 (41.0)	44 (44.4)	53 (54.1)	0.155
Diabetes (%)	11 (10.5)	10 (10.1)	30 (30.6)	**<0.001**
LAD (cm)	3.20 (2.90, 3.50)	3.20 (2.90, 3.40)	3.55 (3.20, 3.90)	**<0.001**
LVDd (cm)	4.50 (4.30, 4.80)	4.70 (4.20, 4.90)	4.75 (4.50, 5.00)	**<0.001**
LVMI (g/m^2)	83.54 (72.57, 92.07)	87.86 (71.55, 99.02)	93.47 (78.44, 110.84)	**<0.001**
RWT	0.42 (0.39, 0.44)	0.42 (0.39, 0.44)	0.42 (0.38, 0.44)	0.977
LVEF (%)	64.40 (63.00, 65.70)	64.40 (63.00, 65.80)	63.50 (61.90, 65.65)	0.079
E/e' ratio	6.60 (5.80, 7.60)	7.10 (6.00, 9.00)	8.40 (6.38, 10.50)	**<0.001**
E/A ratio	1.00 (0.80, 1.30)	0.90 (0.80, 1.30)	0.90 (0.70, 1.20)	0.248
LVH (%)	8 (7.6)	24 (24.2)	33 (33.7)	**<0.001**
eGFR (ml/min/1.73 m²)	98.81 (57.30, 116.30)	93.88 (69.39, 111.38)	86.59 (53.12, 107.41)	0.118
Scr (μmol/L)	79.30 (63.30, 116.80)	74.50 (57.30, 101.50)	82.65 (62.00, 119.75)	0.156
Serum albumin (g/L)	38.60 (36.25, 41.85)	36.60 (30.70, 39.60)	22.40 (18.28, 31.20)	**<0.001**
TG (mmol/L)	1.42 (1.00, 2.01)	1.56 (1.02, 2.27)	1.88 (1.27, 2.50)	**0.007**
TC (mmol/L)	4.57 (3.88, 5.38)	4.78 (4.04, 5.72)	6.16 (5.12, 7.85)	**<0.001**
LDL-C (mmol/L)	2.78 (2.21, 3.35)	2.89 (2.40, 3.50)	3.65 (2.89, 4.76)	**<0.001**
HDL-C (mmol/L)	1.06 (0.94, 1.27)	1.09 (0.95, 1.34)	1.27 (1.07, 1.52)	**<0.001**
Hemoglobin (g/L)	136.80 ± 19.54	128.21 ± 18.81	119.69 ± 23.50	**<0.001**
CRP (mg/L)	2.05 (1.47, 3.59)	1.65 (1.16, 2.73)	1.94 (1.30, 3.06)	0.061
Urinary protein (g/d)	0.59 (0.30, 1.05)	0.91 (0.25, 2.76)	5.45 (1.90, 8.63)	**<0.001**
Urinary sodium (mmol/d)	109.90 (77.10, 151.05)	122.00 (88.90, 165.90)	140.55 (108.40, 192.65)	**0.002**
Urinary potassium (mmol/d)	30.60 (22.80, 39.10)	28.00 (22.40, 35.10)	30.95 (24.60, 41.38)	0.105
OH (L)	−0.80 (−1.30, −0.45)	0.50 (0.20, 0.90)	3.30 (2.00, 5.65)	**<0.001**
ECW (L)	14.10 (12.35, 16.10)	15.00 (13.10, 17.60)	19.10 (15.93, 22.05)	**<0.001**
ICW (L)	19.50 (16.30, 22.40)	18.70 (15.50, 22.50)	19.65 (16.00, 23.10)	0.547
TBW (L)	33.70 (28.70, 38.85)	33.90 (28.20, 39.70)	39.00 (33.30, 45.83)	**<0.001**
ACEI/ARB (%)	46 (43.8)	33 (33.3)	46 (46.9)	0.126
CCB (%)	25 (23.8)	30 (30.3)	39 (39.8)	**0.048**
β-blocker (%)	4 (3.8)	9 (9.1)	12 (12.2)	0.087
Diuretic (%)	2 (1.9)	5 (5.1)	14 (14.3)	**0.002**

CKD, chronic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; CRP c,-reactive protein; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; OH, overhydration; ECW, extracellular water; ICW, intracellular water; TBW, total body water; ACEI/ARB, angiotensin converting enzyme inhibitor/ angiotensin receptor blockers; CCB, calcium-channel blocker. Data were presented as the mean ±SD, the median with interquartile range or counts, and percentages. A two-tailed p < 0.05 was considered statistically significant. The bold values mean that P < 0.05.

age, SBP, MAP, LAD, LVDd, LVMI, RWT, E/e' ratio, urinary protein excretion, and OH were observed in patients with LVH, and the lower levels of LVEF, E/A ratio, eGFR, serum albumin, hemoglobin, and ICW. Moreover, female sex, hypertension, diabetes, FO, and the use of medications containing calcium-channel blocker (CCB) and β-blocker were more prevalent among patients with LVH (all $P < 0.05$, **Table 1**).

Comparisons of Clinical and Laboratory Parameters According to OH Tertiles

On account of the finding that OH level obviously distinguished between patients with and without the occurrence of LVH, we further divided patients into three groups according to OH tertiles, and then compared the clinical and laboratory features among them (**Table 2**). Patients with the highest tertile of OH

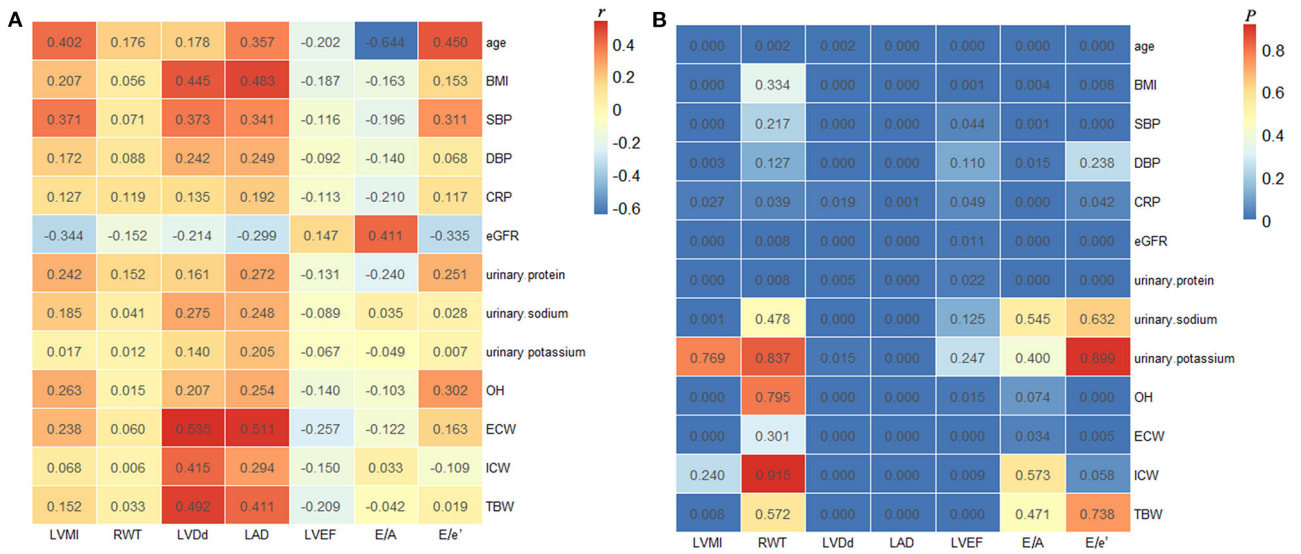

FIGURE 2 | Correlations between echocardiographic findings and clinical and laboratory parameters. The correlation coefficients **(A)** and *P*-values **(B)** of Spearman correlation analyses in all the enrolled patients. LVMI, left ventricular mass index; RWT, relative wall thickness; LVDd, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; OH, overhydration; ECW, extracellular water; ICW, intracellular water; TBW, total body water.

had the highest levels of age, SBP, MAP, LAD, LVDd, LVMI, E/e' ratio, TG, TC, LDL-C, HDL-C, urinary protein excretion, urinary sodium excretion, ECW, and TBW, along with the lowest levels of serum albumin and hemoglobin (all $P < 0.05$). While the levels of age, SBP, MAP, LAD, LVDd, LVMI, E/e' ratio, TG, TC, LDL-C, HDL-C, urinary protein excretion, urinary sodium excretion, ECW, and TBW were the lowest in the lowest tierce, which had the highest serum albumin and hemoglobin levels (all $P < 0.05$). In addition, the incidence of the male sex, diabetes, LVH, and the usage rate of CCB and diuretics were the most prevalent in patients with the highest OH tertile (all $P < 0.05$). However, no significant differences were observed in BMI, eGFR, serum creatinine, CRP, and urinary potassium excretion. Also, the incidence of hypertension and usage rate of β-blocker and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) did not differ among the three groups according to OH tertiles.

Correlations Between Echocardiographic Findings and Clinical and Laboratory Parameters

As shown in **Figure 2**, Spearman correlation analyses indicated that LVMI positively correlated with OH ($r = 0.263$, $P < 0.001$), ECW ($r = 0.238$, $P < 0.001$), TBW ($r = 0.152$, $P = 0.008$), urinary sodium excretion ($r = 0.185$, $P = 0.001$), urinary protein excretion ($r = 0.242$, $P < 0.001$), CRP ($r = 0.127$, $P = 0.027$), age ($r = 0.402$, $P < 0.001$), BMI ($r = 0.207$, $P < 0.001$), SBP ($r = 0.371$, $P < 0.001$), and DBP ($r = 0.172$, $P = 0.003$), whereas it was negatively correlated with eGFR ($r = -0.344$, $P < 0.001$). Besides, OH was positively correlated with LVDd ($r = 0.207$, $P < 0.001$), LAD ($r = 0.254$, $P < 0.001$), and E/e' ratio ($r = 0.302$, $P < 0.001$), it was negatively correlated with LVEF ($r = -0.140$, $P = 0.015$), nevertheless. However, the correlations of LVMI with urinary potassium excretion and ICW, and the correlations of OH with RWT and E/A ratio showed no significant differences.

Overhydration and Left Ventricular Hypertrophy

As shown in **Table 3**, the ORs for the associations between OH and LVH were determined by binary logistic regression models. In unadjusted models, the highest tertile [OR: 6.156 (2.674–14.171), $P < 0.001$] and middle tertile [OR: 3.880 (1.650–9.124), $P = 0.002$] of OH were significantly associated with increased odds of LVH in comparison to the lowest tertile. Also, age, gender, diabetes, SBP, hemoglobin, eGFR, and logarithmic transformation of urinary protein excretion were associated with LVH. After adjustment for age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, eGFR, and logarithmic transformation of urinary sodium and urinary protein in the multivariate logistic regression analyses, increased odds of LVH were also observed in the middle and highest tertiles of OH [OR: 3.082 (1.170–8.114), $P = 0.023$; OR: 4.481 (1.332–15.078), $P = 0.015$, respectively]. Furthermore, the same multivariable-adjusted restricted cubic spline analyses confirmed this finding, which verified a significant non-linear association between OH and LVH (P for non-linear = 0.0363, **Figure 3**). In addition, the multivariate logistic regression analysis demonstrated that age [OR: 1.037 (1.010–1.064), $P = 0.006$], gender [OR: 3.412 (1.472–7.905), $P = 0.004$], and SBP [OR: 1.024 (1.003–1.046), $P = 0.027$] were independently associated with LVH. Nevertheless, other clinical and laboratory parameters containing diabetes, BMI, hemoglobin, serum albumin, eGFR, and logarithmic

TABLE 3 | Univariate and multivariate logistic regression for the association between OH and LVH in all the enrolled patients with CKD.

Variables	Univariate		Multivariate	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
OH (L)				
Tertile 1 (≤-0.1)	1 [reference]		1 [reference]	
Tertile 2 (−0.1–1.2)	3.880 (1.650, 9.124)	0.002	3.082 (1.170, 8.114)	0.023
Tertile 3 (>1.2)	6.156 (2.674, 14.171)	<0.001	4.481 (1.332, 15.078)	0.015
P-value for trend	<0.001		0.015	
Age (years)	1.053 (1.031, 1.075)	<0.001	1.037 (1.010, 1.064)	0.006
Gender (male vs. female)	2.309 (1.315, 4.054)	0.004	3.412 (1.472, 7.905)	0.004
Diabetes (no vs. yes)	3.670 (1.927, 6.988)	<0.001	1.797 (0.768, 4.205)	0.176
BMI (kg/m^2)	1.034 (0.961, 1.112)	0.376	1.064 (0.958, 1.182)	0.245
SBP (mmHg)	1.038 (1.021, 1.054)	<0.001	1.024 (1.003, 1.046)	0.027
Hemoglobin (g/L)	0.966 (0.952, 0.979)	<0.001	0.981 (0.961, 1.002)	0.077
Serum albumin (g/L)	0.970 (0.941, 1.000)	0.052	1.060 (0.986, 1.140)	0.114
eGFR (ml/min/1.73 m²)	0.985 (0.976, 0.993)	<0.001	0.999 (0.985, 1.013)	0.873
Log urinary sodium* (mmol/d)	1.471 (0.398, 5.437)	0.563	0.857 (0.144, 5.105)	0.865
Log urinary protein* (g/d)	2.149 (1.355, 3.406)	0.001	1.622 (0.629, 4.184)	0.317

CKD, chronic kidney disease; OH, overhydration; LVH, left ventricular hypertrophy; BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; OR, odds ratio.

**Urinary sodium and urinary protein were normalized by Log_{10} transformation.*

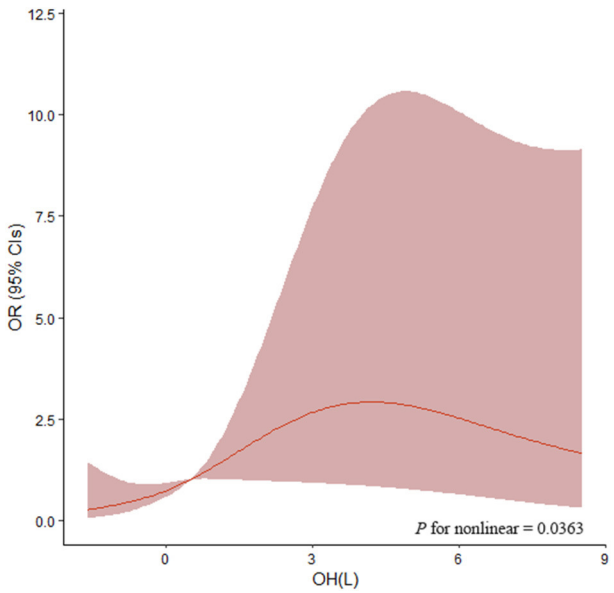

FIGURE 3 | Association of OH with OR of LVH by restricted cubic splines. Restricted cubic splines were plotted using four default knots at the 20th, 40th, 60th, and 80th percentiles. ORs were adjusted for age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, eGFR, and logarithmic transformation of urinary sodium and urinary protein. The *P*-value for non-linear association was 0.0363. OH, overhydration; OR, odds ratio; BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

transformation of urinary sodium excretion and urinary protein excretion did not relate to LVH.

Furthermore, the patients were divided into two groups (group 1: patients with CKD stages 1–2; group 2: patients with CKD stages 3–4) according to CKD stages. In univariate logistic regression analyses, patients with higher tertile of OH showed a higher occurrence of LVH both in patients with stages 1–2 and in patients with stages 3–4. However, increased odds of LVH were observed in the middle and highest tertile of OH [OR: 3.908 (0.975–15.670), $P = 0.054$; OR: 6.347 (1.257–32.054), $P = 0.025$, respectively, P for trend $= 0.026$] only in patients with stages 1–2, with adjustment for age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, and logarithmic transformation of urinary sodium and urinary protein in the multivariate logistic regression analyses.

DISCUSSION

Our study demonstrated a significant association between OH and LVH in patients with non-dialysis CKD. First of all, our results verified LVMI was positively correlated with OH, ECW, TBW, urinary sodium excretion, and urinary protein excretion, whereas it was negatively correlated with eGFR. Furthermore, patients with the highest tertile of OH had the highest prevalence of LVH. Most importantly, both the middle and highest tertile of OH were associated with significantly increased odds of LVH after adjustment for important covariates, which indicated a higher level of OH was an independent determining factor for a higher occurrence of LVH in patients with CKD not on dialysis. In addition, restricted cubic spline analyses unfolded a significant non-linear association between OH and LVH, which suggested OH must be the dummy variable when taken into logistic regression analyses.

On account of reduced glomerular filtration rate, sodium retention, and proteinuria (27, 28), impaired volume homeostasis is one of the main characteristics of CKD, especially in the later

TABLE 4 | Univariate and multivariate logistic regression for the association between OH and LVH in CKD patients with stages 1–2 and 3–4.

Variables	Univariate		Multivariate[a]	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Stages 1–2 ($n = 229$)				
OH (L)				
Tertile 1 (≤-0.1)	1 [reference]		1 [reference]	
Tertile 2 (−0.1–1.1)	6.250 (1.729, 22.597)	0.005	3.908 (0.975, 15.670)	0.054
Tertile 3 (>1.1)	10.185 (2.901, 35.763)	<0.001	6.347 (1.257, 32.054)	0.025
P-value for trend	<0.001		0.026	
Stages 3–4 ($n = 73$)				
OH (L)				
Tertile 1 (≤-0.2)	1 [reference]		1 [reference]	
Tertile 2 (−0.2–1.7)	2.240 (0.611, 8.211)	0.224	1.611 (0.311, 8.347)	0.570
Tertile 3 (>1.7)	4.200 (1.190, 14.829)	0.026	3.394 (0.277, 41.656)	0.339
P-value for trend	0.025		0.348	

[a]*Multivariable: adjusted for age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, and logarithmic transformation of urinary sodium and urinary protein.*
CKD, chronic kidney disease; OH, overhydration; LVH, left ventricular hypertrophy; BMI, body mass index; SBP, systolic blood pressure; OR, odds ratio.

stages. Numerous studies have identified a series of adverse effects of FO on patients with CKD. In patients with CKD, Braam et al. (29) pointed out extracellular volume expansion was associated with increased arterial stiffness and uncontrolled hypertension. Another finding from a prospective observational cohort study of CKD also observed a significant association between higher ECW/TBW ratio and increased 24-h SBP (30). Through our study, we used OH that a new, effective, and representative clinical index to assess volume status. Results showed that patients with a higher level of OH had higher SBP, which was consistent with the aforementioned studies. In addition, several studies reported that higher levels of BP and worse BP control statuses were verified related to LVH (31, 32). In line with this, we found patients with a higher level of SBP manifested increased LVMI. Most importantly, SBP was independently associated with LVH. These observations suggested BP might be an intermediate link between OH and LVH. However, the key finding of this study was that higher OH was related to increased odds of LVH independent of SBP, suggesting other unknown mechanisms were involved.

Accumulated evidence has confirmed inflammation and endothelial dysfunction linked to OH. Increase in inflammatory cytokines containing interleukin (IL)-8, IL-6, and tumor necrosis factor-α (TNF-α) and disorder in endothelial function markers including E-selectin, vascular adhesion molecule (VCAM)-1, and thrombomodulin were detectable in serum or peripheral blood cells in patients with CKD, with some increasing with overhydration (15, 33, 34). Moreover, inflammation is perceived to be probably linked to LVH in patients with CKD. Striking increased levels of serum macrophage migratory inflammatory factor, CRP, IL-1 receptor antagonist, IL-6, and TNF-α were linked to elevated odds of LVH (35, 36). Morphology and function of vascular smooth muscle cells could be altered by inflammation, causing increased arterial stiffness, accelerating the development of LVH. Meanwhile, the subclinical inflammation brings about adverse left ventricular geometry by changing the equilibrium, which adjusts cell growth, apoptosis, phenotype, and matrix turnover of cardiac tissue (37). In addition, Francis et al. (38) perceived inflammation increased bone-derived hormone fibroblast growth factor 23 (FGF23) production, a crucial regulator of mineral metabolism and biomarker of fibrosis, which has been verified to link with LVH in both the animal models and clinical experiment models (39, 40). In this study, CRP, one of the inflammation markers, was also observed positively correlated with LVMI, which suggested inflammation might take part in the latent mechanism of an obvious association between higher OH and a higher level of LVMI in patients with CKD.

Another important finding was that patients with a higher level of OH had higher proteinuria, which was a strong factor in the development of LVH (41). In addition, our findings were consistent with previous studies that elevated OH linked with worse urinary protein (34, 42). On the contrary, heavy proteinuria causes hypoproteinemia, which adds interstitial fluid volume and contracts intravascular volume by a diminished oncotic pressure gradient, inducing renal sodium retention by activation of the renin-angiotensin-aldosterone (43). On the other hand, in the rat's model that was subjected to unilateral nephrectomy and a high-salt diet, it was unfolded that fluid retention was associated with an increase in the renal inflammation with macrophage infiltration and tumor necrosis factor-α overexpression, and glomerular sclerosis (44). Therefore, volume overload might be involved in an aggravating renal injury, which results in massive urinary protein.

Interestingly, our data showed that urinary sodium excretion did not relate to LVH in patients with CKD. Dhingra et al. (45). also observed urinary sodium excretion measured on a spot urine sample was not linked with LVH. Nevertheless, in the study by Zhang et al. (46), the highest tertile of night/day urinary sodium excretion ratio was independently associated with LVH in Chinese patients with CKD. The discrepancy in results may be due to differences in the methods of measurement

and ranges of urinary sodium excretion, study populations, and failure to explore non-linear associations (47). Also, there was no significant association between the severity of CKD and LVH. One example is the wide heterogeneity in the prevalence of LVH, which may be due to the number of patients recruited, the proportion of subjects, the presence of comorbidities, and differences in the stages of CKD. FO is associated with the incidence rate of cardiovascular disease and all-cause mortality in patients with CKD without dialysis. The difference between this study and the previously mentioned results maybe because of the differences in registration criteria and patient cohort composition. Schneider et al. (48) showed that in patients with mild-to-moderate CKD, the volume status assessed by bioelectrical impedance spectroscopy (BIS) was independent of the LV mass measured by MRI. In that study, the eGFR range of enrolled patients was 41–62 ml/min and the urinary ACR range was 8–375 mg/g. They found that increased BMI, hemoglobin, and 24-h SBP were key determinants of LVH. Regression models showed that hydration status, endothelial function, inflammation, or MBD parameters did not increase the significance of LVH models.

In addition, our study found that a significant association between OH and LVH was observed in CKD patients with stages 1–2 but not in stages 3–4. Numerous studies revealed that not only FO, but also renin-angiotensin-aldosterone system (RAAS) system activation, endothelial dysfunction, and proinflammatory factors overexpression existed in CKD with moderate-to-serious renal dysfunction, which was related to LVH (15, 34, 49–51). In that case, changes in OH alone were not enough to increase the prevalence of LVH, which might explain why OH did not associate with LVH in CKD patients with stages 3–4. In addition, the numbers with CKD stages 3–4 were much lower than stages 1–2, causing this subgroup analysis underpowered, which was also the explanation of the discrepancy in associations between OH and LVH in CKD stages 1–2 and stages 3–4. Intriguingly, findings showed that the relationship between OH and LVH was stronger where the CKD is less severe (stages 1–2), and with larger ORs. Moreover, there were still 33.2% of CKD patients with stages 1–2 suffering from overhydrated (OH $\geq$ 1.1 L). Compared with patients without overhydrated, urinary sodium excretion, an important means to measure dietary salt intake, was significantly increased in these patients with overhydrated, which reflected higher salt and water retention. Apart from that, an article published in JAMA pointed out higher urinary sodium excretion was associated with an increased risk of cardiovascular disease in CKD patients (52). All these phenomena suggest that volume management should be initiated even in the patients with early CKD, such as dietary restriction of salt.

This study has several limitations. First, this study was cross-sectional observational research so causation could not be inferred. Moreover, while covariates affecting LVH had been adjusted as much as we could, residual confounding was still a latent limitation. Second, this study was conducted in a single center, and the sample size was small as compared with the article published in JAMA (52). Statistical power might be reduced when we performed subgroup analysis based on eGFR due to the limited samples. In particular, the sample size of the two groups was not balanced (**Table 4**). More samples are required in future studies to verify the results of this association in CKD stages 1–2. Third, most patients lacked other laboratory indexes reflecting fluid status and cardiac function, such as amino-terminal pro-B-natriuretic peptide (NT-proBNP), and cardiac troponin T(cTnT), which cannot be included in the subsequent analysis. Further multiple-center and controlled prospective studies on large groups of patients are needed.

CONCLUSION

In conclusion, this study demonstrated that a higher level of OH was associated with a higher occurrence of LVH in patients with CKD not on dialysis, especially in CKD patients with stages 1–2. This association was significant regardless of age, gender, diabetes, BMI, SBP, hemoglobin, serum albumin, eGFR, urinary sodium excretion, and urinary protein excretion.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (approval number: No. 2018-SR-250). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LS designed and conducted the research, and analyzed the data. QL, ZS, and SD contributed to the writing and critical review of the manuscript. GN, JD, CZ, MZ, BS, YY, and NW reviewed the manuscript. CX and HM coordinated and conceived the study and revised the manuscript. BZ is the guarantor of this study and had complete access to all the data in the study. All authors have read the final manuscript and approved the submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.761848/full#supplementary-material

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Clinical Significance of Volume Status in Body Composition and Physical Performance Measurements in Hemodialysis Patients

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Introduction: This study aimed to evaluate the association between volume status and body composition or physical performance measurements in hemodialysis patients.

Methods: A total of 84 patients were enrolled in this study. The participants were divided into tertiles based on the edema index (extracellular water/total body water): low, middle, and high tertiles. Serum albumin and serum high-sensitivity C-reactive protein levels were measured. The appendicular lean mass index (ALM/Ht^2, kg/m^2) was measured using dual-energy X-ray absorptiometry. The thigh muscle area index (TMA/Ht^2, cm^2/m^2) was measured using CT. Extracellular and total body water and phase angles were obtained using bioimpedance analysis. The results of the subjective global assessment (SGA), hand-grip strength (HGS), gait speed (GS), short physical performance battery (SPPB), sit-to-stand for 30-second (STS30) test, timed up and go (TUG), sit-to-stand test performed five times (STS5), and 6-minute walk (6-MW) tests were also evaluated.

Results: On the univariate analysis, the SGA score and phase angle in the high tertile group were the lowest among the three groups. On multivariate analysis, TMA/Ht^2 and phase angle in the high tertile were the lowest among the three groups. Inverse correlations were observed between edema index and TMA/Ht^2, SGA score, phase angle, HGS, GS, SPPB, STS30, or 6-MW. Positive correlations were observed between the edema index and the STS5 or TUG test. The sensitivity and specificity for predicting low GS were 34.5 and 89.7%, respectively. The values for predicting low SPPB were 68.0 and 79.7%, respectively.

Conclusion: This study demonstrates that high volume status may be associated with decreased muscle mass and physical performance regardless of inflammatory or nutritional status.

Keywords: physical performance, hemodialysis, edema, nutrition, muscle mass

INTRODUCTION

The number of patients undergoing hemodialysis (HD) has increased as life expectancy and the incidence of chronic diseases such as diabetes mellitus (DM) or hypertension has increased (1–3). HD patients are inherently prone to hypervolemic status due to a decrease in renal function. Hypervolemia in HD patients is associated with increased blood pressure and high cardiovascular mortality or morbidity (4, 5). Volume control in HD patients is an important issue. Recent studies have shown that hypervolemia has indirect effects on the cardiovascular system and is associated with malnutrition and/or inflammation (6).

Hypervolemia can lead to inflammation. Although the definite pathogenesis between the two variables remains unclear, some evidence has shown that the possible pathogenesis includes endotoxin translocation *via* the edematous bowel or a decrease in splanchnic blood flow by intradialytic hypotension or high ultrafiltration volume (6, 7). Consequently, inflammation can lead to malnutrition, particularly a decrease in muscle mass, which is associated with a higher prevalence of sarcopenia in patients with dialysis than in the general population (8). Some studies have reported an association between volume status and inflammation or biochemical nutritional markers. However, biochemical markers are not accurate indicators of hypervolemic status. For example, serum albumin is generally a surrogate marker of nutritional status, but serum albumin is decreased by hypervolemia and/or inflammation regardless of nutritional status (9). Therefore, body composition analysis or physical performance may be a more accurate method for predicting the changes in muscle mass or quality. This study aimed to evaluate the association between volume status and body composition or physical performance.

METHODS

Study Population

This was a retrospective and cross-sectional study based on the analysis of an existing dataset (10). Briefly, this study was performed in a tertiary medical center between September 2012 and March 2015. We identified all adult patients undergoing HD, patients who had dialysis vintage of $\geq$6 months, patients who were able to ambulate without an assistive device, and patients who were not hospitalized within 3 months before enrollment. A total of 84 patients were enrolled in this study. Informed consent was obtained from all participants. This study was approved by the institutional review board of a tertiary medical center. All the investigations were conducted according to the principles of the Declaration of Helsinki. None of the participants were taking opioids, antihistamines, or antidepressants, which can be associated with decreased physical performance and cognitive function. The participants were divided into tertiles based on the edema index: low, middle, and high tertiles.

Study Variables

Patients' demographic data were obtained: sex, age, underlying diseases of the end-stage renal disease, and dialysis duration. The following laboratory data were collected: hemoglobin (g/dl), albumin (g/dl), high-sensitivity C-reactive protein (hs-CRP) (mg/dl), blood urea nitrogen (BUN) (mg/dl), creatinine (mg/dl), aspartate transaminase (AST) (U/L), alanine transaminase (ALT) (U/L), calcium (mg/dl), phosphorus (mg/dl), sodium (mEq/l), potassium (mEq/l), chloride (mEq/l), intact parathyroid hormone (i-PTH) (pg/ml), total cholesterol (mg/dl), and $spKt/V_{urea}$.

Serum albumin and hs-CRP levels were measured using an Olympus AU4500 automatic chemical analyzer (Olympus, Tokyo, Japan). Serum albumin level was measured using the bromocresol green method. Serum albumin and hs-CRP levels were averaged over three measurements. $spKt/V_{urea}$ was calculated using the Daugirdas' formula (11).

Assessment of Body Composition Measurements and Subjective Global Assessment

In this study, muscle mass was measured using whole-body dual-energy X-ray absorptiometry (DEXA) (GE Medical Systems Lunar, Madison, Wisconsin, USA) and CT (Aquilion ONE; Toshiba Medical Systems Corporation, Tokyo, Japan) of the thigh. Two measurements were performed while the patient was in the supine position, wearing a light gown midweek following the HD session. Appendicular lean mass index (ALM/Ht^2, kg/m^2), total fat mass index (FM/Ht^2, kg/m^2), and T-score were measured using DEXA. ALM/Ht^2 and FM/Ht^2 were calculated as the sum of the muscle mass of both extremities or the total fat mass per height squared. The bone mineral density of the whole body was measured, and the *T*-score was defined as the bone mineral density of the whole body using the International Society for Clinical Densitometry guidelines (12).

After the DEXA measurements, the patient underwent a mid-thigh CT scan. With regard to CT, axial images were obtained at the midpoint of a line extending from the superior border of the patella to the greater trochanter (3 mm thickness, 5 slices). The images were analyzed using image analysis software (ImageJ 1.45S, National Institutes of Health, Bethesda, Maryland, USA). The values were divided by height squared, and the thigh muscle area index (TMA/Ht^2, cm^2/m^2) was calculated. In addition, the intermuscular fat area (IMFA) index was obtained from the same image.

The edema index, visceral fat area (VFA) (cm^2), and phase angle were measured using multifrequency bioimpedance analysis (BIA) (InBody, Seoul, Korea). Extracellular and total body water was obtained using BIA. The edema index was defined as the ratio of extracellular water to total body water. Briefly, the BIA machine presented an edema index, and the abnormal cut-off value was obtained from the mean and SD of a healthy population with large sample size. The normal edema index was defined as the mean $\pm$ 2SD (interval of mean $\pm$ 2 SD, 0.300–0.350). Patients with an edema index $>$ 0.350 were classified as having hypervolemia. However, the edema index is a continuous variable that should be considered for some biased measurements on a single measurement. Therefore, categorization by tertiles or quartiles rather than dichromatic approaches using a single cut-off value would be helpful in

identifying trends according to a continuous variable. Therefore, we divided the patients into tertiles based on limited sample size. Levels of the edema index in low, middle, or high tertile were 0.338 ± 0.010 (interval, 0.318–0.351), 0.356 ± 0.003 (interval, 0.352–0.361), and 0.370 ± 0.007 (interval, 0.363–0.388), respectively.

Body mass index (BMI) (kg/m^2) was calculated using body weight per height squared. Subjective global assessment (SGA) is a scoring system consisting of seven items: weight loss, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, decreased fat, or muscle (13). The 7-point SGA scale was used and defined; patients with 6–7 points were defined as well-nourished (14). Therefore, patients with an SGA score <6 points were categorized into the malnourished SGA group.

Assessment of Handgrip Strength and Physical Performance

Hand-grip strength (HGS) was measured using a manual hydraulic dynamometer (Jamar hydraulic hand dynamometer; Sammons Preston, Chicago, Illinois, USA). Each participant performed three trials on the dominant hand and the maximum strength was recorded. Gait speed (GS) was measured according to a standard protocol; the participants were asked to walk a 4-m distance and the time taken (in seconds) to walk the distance was recorded. The short physical performance battery (SPPB) test consisted of GS, a sit-to-stand test performed five times (STS5), and balance tests and was calculated using the previously defined methods (scores ranged between 0 and 12) (15). STS5 was measured according to a previous protocol; each participant was seated on a chair with arms crossed and hands touching the shoulders (16). The participants were asked to stand up and sit down five times as quickly as possible, and the time it took for the participants to perform the tasks was recorded (in seconds).

For the sit-to-stand for 30-s (STS30), the participants were seated on a chair with their arms crossed and hands touching the shoulders. Scores were defined as the number of stands a person could complete in 30 s without using their arms to stand (17). For the 6-min walk test (6-MWT), the participants were asked to walk at their usual pace for 6 min and the distance they covered was recorded in meters (18). For the timed up and go (TUG) test, the participants were instructed to rise from an armchair, walk 3 m, turn around, return, and sit down (19). The time it took for the participants to perform the tasks was recorded (in seconds). The average step was measured using a pedometer. Moreover, a low group was defined based on their scores on the SPPB and GS tests. The low SPPB group was defined as participants with a score of ≤10, while the low GS group was defined as those with a speed of ≤0.8 m/s (20).

The presence of frailty was defined using the Johansen method (21). Briefly, slowness, poor endurance, physical inactivity, and unintentional weight loss are components of frailty. The presence of each frailty component was scored as 1, and the individual scores for each of the four components were summed. Participants with ≥3 points were defined as having frailty. Disability was measured by asking four questions related to the activities of daily living to determine whether the patient required

TABLE 1 | Participants' clinical characteristics.

	Low tertile (n = 26)	Middle tertile (n = 29)	High tertile (n = 29)	P-value
Sex (male, %)	13 (50.0%)	14 (48.3%)	17 (58.6%)	0.702
Age (years)	50.5 ± 12.7	58.5 ± 9.7[a]	59.9 ± 11.6[a]	0.006
DM as underlying disease of ESRD (%)	7 (26.9%)	16 (55.2%)	21 (72.4%)	0.003
Dialysis vintage (years)	4.7 ± 5.3	3.9 ± 5.0	5.0 ± 5.3	0.720
Hemoglobin (mg/dL)	11.1 ± 0.6	10.9 ± 0.6	10.9 ± 0.6	0.398
hs-CRP (mg/dL)	0.16 ± 0.10	0.18 ± 0.15	0.21 ± 0.15	0.610
Blood urea nitrogen (mg/dL)	63.3 ± 16.5	55.9 ± 16.5	55.9 ± 16.5	0.168
Creatinine (mg/dL)	11.1 ± 3.3	10.0 ± 1.8	9.9 ± 2.5	0.177
Serum albumin (g/dL)	3.8 ± 0.3	3.9 ± 0.2	3.8 ± 0.3	0.662
Aspartate transaminase (U/L)	16.0 ± 3.6	19.3 ± 6.1	18.1 ± 6.9	0.104
Alanine transaminase (U/L)	14.7 ± 7.2	15.2 ± 6.3	17.5 ± 8.8	0.335
Serum calcium (mg/dL)	8.3 ± 0.8	8.3 ± 0.5	8.5 ± 0.7	0.501
Serum phosphorus (mg/dL)	6.7 ± 0.4	6.6 ± 0.4	6.6 ± 0.4	0.442
Serum sodium (mEq/L)	137.9 ± 2.6	136.9 ± 2.8	138.1 ± 2.8	0.223
Serum potassium (mEq/L)	4.9 ± 0.5	5.1 ± 0.4	5.0 ± 0.7	0.403
Serum chloride (mEq/L)	98.8 ± 3.4	98.0 ± 3.2	98.7 ± 3.7	0.645
Intact parathyroid hormone (pg/mL)	281.5 ± 198.3	240.4 ± 144.0	270.6 ± 207.4	0.691
Total cholesterol (mg/dL)	162.2 ± 32.4	151.1 ± 34.1	149.2 ± 36.1	0.326
spKt/V_{urea}	1.43 ± 0.3	1.35 ± 0.4	1.32 ± 0.2	0.417

Data are expressed as mean ± SD for continuous variables and numbers (percentage) for categorical variables. P-values were tested by one-way ANOVA, followed by a post-hoc Tukey comparison for continuous variables, and Pearson's χ^2 or Fisher's exact tests for categorical variables.

[a] *$P < 0.05$ compared with low tertile.*

DM, diabetes mellitus; ESRD, end-stage renal disease; hs-CRP, high-sensitivity C-reactive protein.

assistance when feeding, dressing/undressing, getting in/out of bed, or taking a bath/shower (22). Each question required one of the following three responses: no help, some help, or full help. Disability was defined as requiring some or full assistance when performing two or more activities in daily living domains. In addition, we determined whether the patient had limitations in vigorous or moderate physical activity. Vigorous or moderate physical activity was defined based on the WHO guidelines (23). The participant selected one of the following three answers: severe limitation, some limitation, or no limitation.

Statistical Analysis

Data were analyzed using the statistical software SPSS version 25 (Chicago, Illinois, USA). Categorical variables were expressed as counts (percentages) and were analyzed using the chi-square test. Continuous variables were expressed as mean ± SD or SE. For continuous variables, means were compared using one-way ANOVA, followed by a *post-hoc* Tukey comparison, and analysis of covariance for multivariate analysis. The correlation between two continuous variables was assessed using Pearson's and partial correlation analyses. The patient survival analysis was compared using the Cox regression analysis. The multivariate analysis was adjusted for age, sex, and DM. The level of statistical significance was set at $P < 0.05$.

RESULTS

Participants' Clinical Characteristics

The mean age of the low tertile group was lower than that of the other tertile groups (**Table 1**). The proportion of DM as an underlying disease increased as the edema index tertile increased; the proportion of chronic glomerulonephritis was the greatest in the low tertile (**Supplementary Table 1**). The distribution of underlying diseases of end-stage renal disease was significantly different among the tertiles ($P = 0.019$). The number of male participants was similar among the three groups. There were no significant differences in hemoglobin, hs-CRP, BUN, creatinine, AST, ALT, serum calcium, phosphorus, sodium, potassium, chloride, i-PTH, total cholesterol, and spKt/V_{urea} levels among the three groups.

Association Between Edema Index and Body Composition, Nutritional, or Physical Performance Indices

On the univariate analysis, the SGA score and phase angle in the high tertile were the lowest among the three groups (**Table 2**). On multivariate analysis, TMA/Ht^2 and phase angle in the high tertile were the lowest among the three groups. There were no significant differences in BMI, ALM/Ht^2, FM/Ht^2, VFA, T-score of BMD, and serum albumin levels among the three groups. The IMFA index was greatest in the high tertile among tertiles in univariate and multivariate analyses.

HGS, GS, SPPB, STS30, and 6-MWT in the high tertile were the lowest among the three groups in the univariate and multivariate analyses (**Table 3**). There was no significant difference in the average number of steps among the three groups. TUG and STS5 in the high tertile were the greatest among the three groups in the univariate analysis but not in the multivariate analysis. The phase angle values in the low, middle, and high tertiles were 5.9 ± 0.9, 4.7 ± 0.2, and 4.2 ± 0.8, respectively ($P < 0.001$). The multivariate analyses showed trends similar to those from the univariate analysis.

The correlations between the edema index and various indices are shown in **Supplementary Table 2**. Inverse correlations were observed between the edema index and TMA/Ht^2, SGA score, phase angle, HGS, GS, SPPB, STS30, or 6-MWT. Positive correlations were observed between the edema index and the STS5 or TUG test.

The number of patients with disability in the low, middle, and high tertiles was 1 (3.8%), 1 (3.4%), and 3 (10.3%), respectively ($P = 0.465$). The prevalence of frailty in the low, middle, and high tertiles was 3 (11.5%), 7 (24.1%), and 14 (48.3%), respectively ($P = 0.009$). Those with the low GS in low, middle, or high tertiles were 4 (15.4%), 6 (20.7%), and 17 (58.6%), respectively ($P = 0.001$). Those with low SPPB in the low, middle, or high tertiles were 2 (7.7%), 6 (20.7%), and 17 (58.6%), respectively ($P < 0.001$).

TABLE 2 | Comparison of body composition and nutritional indices according to edema index tertile.

	Low tertile	Middle tertile	High tertile	*P*-value
Univariate				
Body mass index (kg/m^2)	23.3 ± 3.0	23.5 ± 3.4	24.3 ± 4.3	0.538
ALM/Ht^2 (kg/m^2)	6.7 ± 1.1	6.5 ± 0.9	6.6 ± 0.9	0.685
FM/Ht^2 (kg/m^2)	6.7 ± 2.9	6.7 ± 2.8	6.8 ± 3.5	0.995
TMA/Ht^2 (cm^2/m^2)	39.1 ± 8.1	37.2 ± 6.4	34.6 ± 6.1	0.052
Visceral fat area (cm^2)	88.0 ± 23.6	96.8 ± 25.8	104.3 ± 30.6	0.087
T-score of BMD	−0.9 ± 1.7	−0.9 ± 1.4	−1.1 ± 1.4	0.845
SGA score	6.1 ± 1.0	5.7 ± 1.0	5.3 ± 0.9[a]	0.009
Serum albumin (g/dL)	3.8 ± 0.3	3.9 ± 0.2	3.8 ± 0.3	0.662
Phase angle	5.9 ± 0.9	4.7 ± 0.5[a]	4.2 ± 0.8[a,b]	<0.001
IMFA index (cm/m^2)	1.6 ± 0.8	1.7 ± 1.0	2.6 ± 2.0[a,b]	0.015
Multivariate				
Body mass index (kg/m^2)	23.5 ± 0.8	23.5 ± 0.7	24.1 ± 0.7	0.797
ALM/Ht^2 (kg/m^2)	6.6 ± 0.2	6.5 ± 0.1	6.6 ± 0.2	0.873
FM/Ht^2 (kg/m^2)	6.7 ± 0.6	6.6 ± 0.5	6.8 ± 0.6	0.943
TMA/Ht^2 (cm^2/m^2)	39.1 ± 1.4	37.5 ± 1.2	34.3 ± 1.2[a,b]	0.041
Visceral fat area (cm^2)	94.8 ± 5.2	96.0 ± 4.6	99.1 ± 4.8	0.827
T-score of BMD	−1.0 ± 0.3	−0.8 ± 0.3	−1.0 ± 0.3	0.786
SGA score	6.0 ± 0.2	5.8 ± 0.2	5.4 ± 0.2	0.093
Serum albumin (g/dL)	3.8 ± 0.1	3.9 ± 0.0	3.9 ± 0.1	0.266
Phase angle	6.0 ± 0.1	4.7 ± 0.1[a]	4.1 ± 0.1[a,b]	<0.001
IMFA index (cm/m^2)	1.7 ± 0.3	1.6 ± 0.3	2.6 ± 0.3[a,b]	0.037

Data were expressed as the mean ± SD for univariate analysis and the mean ± SE for multivariate analysis. Univariate analysis was performed using one-way ANOVA, followed by a post-hoc Tukey comparison, and multivariate analysis was performed using analysis of covariance and adjusted for age, sex, and diabetes mellitus.

[a] $P < 0.05$ compared with low tertile.

[b] $P < 0.05$ compared with middle tertile.

ALM/Ht^2, appendicular lean mass per height squared; FM/Ht^2, fat mass per height squared; TMA/Ht^2, thigh muscle area per height squared; BMD, bone mineral density; SGA, subjective global assessment; IMFA, intermuscular fat area.

TABLE 3 | Comparison of physical performance indices according to edema index tertile.

	Low tertile	Middle tertile	High tertile	*P*-value
Univariate				
HGS	29.4 ± 9.3	26.0 ± 5.5	23.1 ± 5.8[a]	0.005
Gait speed	0.99 ± 0.17	0.96 ± 0.15	0.81 ± 0.22[a,b]	0.001
SPPB	11.6 ± 0.9	11.4 ± 0.9	9.7 ± 2.1[a,b]	<0.001
STS5	7.2 ± 2.1	8.2 ± 2.4	11.1 ± 9.7[a]	0.046
STS30	20.7 ± 6.0	17.9 ± 4.7	15.2 ± 5.2[a]	0.001
6-MWT	505.4 ± 87.7	482.2 ± 92.7	394.1 ± 124.6[a,b]	<0.001
TUG	6.3 ± 1.6	7.1 ± 1.6	8.5 ± 2.2[a,b]	<0.001
Average steps	5,882 ± 2,659	5,073 ± 3,509	3,862 ± 3,815	0.097
Multivariate				
HGS	28.6 ± 1.2	26.6 ± 1.0	23.2 ± 1.1[a,b]	0.005
Gait speed	0.96 ± 0.04	0.97 ± 0.03	0.82 ± 0.03[a,b]	0.002
SPPB	11.3 ± 0.3	11.5 ± 0.3	9.9 ± 0.3[a,b]	<0.001
STS5	8.0 ± 1.3	8.0 ± 1.1	10.5 ± 1.2	0.227
STS30	20.0 ± 1.1	18.2 ± 1.0	15.5 ± 1.0[a,b]	0.018
6-MWT	478.0 ± 20.0	491.7 ± 17.5	409.1 ± 18.2[a,b]	0.004
TUG	6.8 ± 0.4	6.9 ± 0.3	8.3 ± 0.3[a,b]	0.005
Average steps	5,939 ± 757	5,040 ± 646	3,845 ± 683	0.149

Data are expressed as mean ± SD for univariate analysis and the mean ± SE for multivariate analysis. Univariate analysis was performed using one-way ANOVA, followed by a post-hoc Tukey comparison, and multivariate analysis was performed using analysis of covariance and adjusted for age, sex, and diabetes mellitus.

[a]P < 0.05 compared with low tertile.

[b]P < 0.05 compared with middle tertile.

HGS, handgrip strength; SPPB, short physical performance battery; STS5, five times sit-to-stand test; STS30, sit-to-stand for 30-s test; 6-MWT, 6-min walk test; TUG, timed up-to-go test.

The discrimination power of the edema index for predicting disability, frailty, low GS, or low SPPB was determined using receiver operating characteristic (ROC) analysis. The area under the ROC, sensitivity, and specificity for predicting disability were 0.691 (0.581–0.787), 50 (14.7–94.7)%, and 79.9 (69.2–88.0)%, respectively ($P = 0.183$). Those for predicting frailty were 0.713 (0.604–0.806), 66.7 (44.7–84.4)%, and 71.7 (58.6–82.5)%, respectively ($P < 0.001$). Those for predicting low GS were 0.641 (0.529–0.743), 34.5 (22.2–48.6)%, and 89.7 (72.6–97.8)%, respectively ($P = 0.025$). Those for predicting low SPPB were 0.791 (0.688–0.872), 68.0 (46.5–85.1)%, and 79.7 (67.2–89.0)%, respectively ($P < 0.001$).

Supplementary Table 3 shows the questionnaire results of the subjective evaluation of the limitations in physical activity. High tertile was associated with a higher limitation of physical activity compared with the other tertiles. In addition, in univariate analysis, the odds ratio of high tertile of the edema index was 2.76 (95% CI, 0.97–7.84; $P = 0.058$) for low GS, 8.32 (95% CI, 2.91–23.85; $P < 0.001$) for low SPPB, 4.20 (95% CI, 1.55–11.42; $P = 0.005$) for frailty, 3.06 (95% CI, 0.48–19.44; $P = 0.236$) for disability, and 2.33 (95% CI, 0.95–5.85; $P = 0.071$) for malnourished SGA. In multivariate analyses, the odds ratio of high tertile of the edema index was 3.29 (95% CI, 0.98–11.02; $P = 0.053$) for low GS, 6.30 (95% CI, 2.08–19.11; $P = 0.001$) for low SPPB, 3.00 (95% CI, 1.01–8.88; $P = 0.047$) for frailty, 1.26 (95% CI, 0.16–10.23; $P = 0.828$) for disability, and 1.83 (95% CI, 0.67–4.98; $P = 0.237$) for malnourished SGA.

Subgroup Analyses by DM and Age

For participants without DM, multivariate analyses showed inverse correlations between the edema index and TMA/Ht^2, SGA score, phase angle, HGS, GS, SPPB, or STS30 (**Supplementary Table 4**). Positive correlations were observed between the edema index and the STS5 or TUG test. For participants with DM, multivariate analyses showed inverse correlations between the edema index and phase angle, SPPB, STS30, or 6-MWT. Positive correlations were observed between the edema index and the STS5 or TUG test.

For participants aged < 65 years, the multivariate analyses showed inverse correlations between edema index and TMA/Ht^2, SGA score, phase angle, HGS, GS, SPPB, STS30, or 6-MWT (**Supplementary Table 5**). Positive correlations were observed between the edema index and the STS5 or TUG test. For participants aged ≥65 years, multivariate analyses showed inverse correlations between the edema index and SGA score, phase angle, GS, or average steps.

For participants <3 years of dialysis vintage ($n = 42$), the multivariate analyses showed inverse correlations between the edema index and phase angle, HGS, SPPB, STS30, or average steps (**Supplementary Table 6**). For participants ≥3 years of dialysis vintage ($n = 42$), the multivariate analyses showed inverse correlations between the edema index and TMA/Ht^2, SGA score, phase angle, GS, SPPB, STS30, or 6-MWT.

Survival Analyses According to Variables

The mean follow-up durations in the low, middle, and high tertiles were 646 ± 317, 650 ± 321, and 491 ± 356 days ($P = 0.128$). Survival analyses were performed using Cox regression (**Supplementary Table 7**). The univariate Cox regression analyses showed that an increase in 0.01 unit of edema index was associated with a 2.19 higher hazard ratio and the multivariate analysis showed a 2.26 higher hazard ratio according to an increase in 0.01 unit of edema index. On the univariate analysis, increases in GS, STS30, and 6-MWT were associated with a lower hazard ratio. The multivariate analyses showed trends similar to those from the univariate analyses.

DISCUSSION

In this study, the participants were divided into three tertiles according to the edema index. Baseline age and the presence of diabetes differed among the three groups. Multivariate analyses adjusted for age, sex, and presence of DM were performed. The results of multivariate analyses showed that the edema index was associated with TMA/Ht^2, phase angle, and most physical performance measurements but not with BMI, FM/Ht^2, ALM/Ht^2, VFA, T-score of BMD, SGA score, hs-CRP, and serum albumin level. In addition, correlation analyses were performed using the edema index as a continuous variable and subgroup analyses for the presence of DM or age. Results from the correlation and subgroup analyses showed similar trends. The discrimination power of the edema index for predicting frailty,

low GS, or low SPPB was relatively favorable. Furthermore, this study showed an association between edema index and mortality.

First, we evaluated the association between edema index and body composition measurements. There was no significant difference in visceral fat, total fat mass index, or bone components among the three groups. Muscle mass measurement among the three groups was different in TMA/Ht^2 alone using CT and not in ALM/Ht^2 using DEXA. Using DEXA, lean mass was measured as all masses except bone and fat. It includes the skin and fat-free mass of the adipose tissue (24). Volume overload can distribute muscle mass and skin, which leads to an overestimation of lean mass using DEXA. However, muscle mass using CT can exclude overhydrated skin and fat-free mass of adipose tissue. In this data, the non-difference in ALM/Ht^2 using DEXA may be associated with the overestimation of measurements according to volume overload. The difference was clearer for measurements using CT than for DEXA.

Other important results of this study were FM, IMFA indices, and mortality. Fat measurements using CT or DEXA were relatively accurate, regardless of the volume effects. There was no significant difference in the FM index among tertiles, but the IMFA index was the greatest in the high tertile among tertiles. Hypervolemia is associated with inflammation, which can lead to insulin resistance and/or cardiovascular disease. Previous studies have shown that volume overload contributes to the pathogenesis of insulin resistance in HD patients, which results in a high prevalence of cardiovascular disease (6, 25, 26). This study revealed that patients with a high-volume status had a greater IMFA index than those with other tertiles. This may be associated with decreased muscle function (27). However, a difference in the FM index was not obtained among tertiles. The combination effect with an increase in fat by insulin resistance and decrease in fat by malnutrition would be associated with non-difference in FM index among tertiles.

In addition, we compared the associations between various variables and mortality rates. An increase in the edema index was associated with a high mortality on univariate and multivariate analyses. High mortality in patients with a high edema index would be associated with combined effects, including cardiovascular effects, inflammation, and/or malnutrition. An increase in GS, STS30, or 6-MWT was associated with low mortality in the univariate and multivariate analyses. These findings reveal that favorable physical performance is associated with improved patient survival. However, some indicators such as HGS, SPPB, STS5, TUG, and muscle mass indices were not statistically significant. Various factors, such as small differences in variables between participants, small sample size, or overestimated muscle mass measurements due to volume overload, may lead to statistical non-significance.

Another important result in this study is the inverse association between the phase angle and volume status. Previous studies have shown an association between phase angle and prognosis, including nutritional status and mortality in dialysis patients (28, 29). The phase angle is originally associated with cellularity and water content to cell mass, and a high phase angle reveals high cellularity and low extracellular water to intracellular water ratio (30). Therefore, the phase angle can be influenced by the nutritional and volume status in dialysis patients. The slope of extracellular water to body weight in patients with dialysis increases more steeply compared with normovolemia participants (31). These results reveal that the edema index increased as the volume overloading increased, which resulted in a decrease in the phase angle. In addition, patients with hypervolemic can be associated with malnutrition, which leads to cellular degradation, which, in turn, results in a low phase angle through low cellularity. Our results showed that the phase angle decreased as the edema index tertile increased, which was similar to the results of previous studies.

This study showed that the association between the edema index and SGA was only modest, and there was no association between the edema index and serum albumin or hs-CRP. Previous studies have shown a positive association between volume overload and inflammation or hypoalbuminemia in HD patients (26, 32, 33). The association between volume status and serum albumin level was bidirectional. Volume overloading can lead to underestimation of the actual serum albumin level, and hypoalbuminemia can be associated with increased extracellular water *via* decreased osmotic pressure. The inverse association between the two variables would be reasonable. However, this study did not show a strong association among these variables, which may be due to the relatively stable volume status in our cohort and the measurement of two variables in the post-HD period. As the volume overload increased, the effect on serum albumin of volume increased. We measured the edema index post-HD, and the edema index interval in our cohort was 0.318–0.388 (normal range proposed from BIA: 0.300–0.350). Therefore, the post-HD edema index in one-third of our cohort was within the normal range. In the post-HD period, differences between patients with the lowest and highest values would not be sufficiently large to induce statistical significance. However, the trends for hs-CRP were similar to those for the edema index. If these variables were measured during the pre-HD period, statistical significance may have been obtained.

This study showed a negative association between the edema index and nutritional or inflammatory indices, but physical performance indices and muscle mass decreased as the edema index increased. These findings reveal that the occurrence of non-severe overhydration in our cohort did not lead to biochemical changes, but this can lead to a decrease in physical performance, which is associated with a decrease in muscle mass or function. Subjective sensation for limitation of physical activity was also greater in the high tertile group than in the other tertile groups.

In this study, the number of participants differed among the three groups. The edema index was calculated as extracellular water/total body water, and the same absolute value was difficult to obtain. However, the BIA machine expresses the edema index to only three decimal points in error or validity to calculate the edema index. Some patients had the same edema index values, despite having different absolute values. Considering the limitations of categorical groups, we performed additional analyses for the association

between edema index values as continuous variables and various indices.

The strength of this study is its comprehensive evaluation of physical performance. Physical performance is inversely associated with muscle strength and/or mass (34, 35). However, a decrease in muscle strength occurs earlier than a decrease in muscle mass. Decreased physical performance is correlated with decreased muscle strength, but the association is non-linear. Physical performance is more likely to be associated with muscle quality than muscle mass *per se*. In addition, physical performance would be generally influenced by various factors, such as lifestyle and biological and psychological factors. Beyond muscle mass or strength, abnormalities in motor coordination, excitation-contraction coupling, and skeletal integrity can lead to a decrease in physical performance. Therefore, a decrease in physical performance can develop before or without a decrease in muscle mass or strength. In this study, the strong positive association between the edema index and strength or physical performance indices, and the weak positive association between the edema index and muscle mass index may be parallel to these concepts.

This study has some inherent limitations. First, this study was performed at a single center and had a small sample size. This study was a cross-sectional retrospective study using a cohort from a previous study (10). This design does not evaluate the causal relationship among variables. In addition, the small sample size could limit the adjustment of confounding variables. However, there were significant differences in baseline age and the presence of DM among the tertiles in this study. Differences in two variables can lead to a statistical bias, and sex can also be considered as a confounding factor for the comparison of body composition, nutrition, and physical performance indicators. The results may not be accurate, without adjustment for these variables. Statistical significance was obtained despite the small sample size. Second, the volume status in this study was measured post-HD. Measurements including volume status, muscle mass, strength, and physical performance were evaluated at midweek following the HD session. Single measurements may not completely reflect the actual volume status. In addition, this study did not evaluate the association between longitudinal changes in volume status, such as before and after HD session, or changes in volume status after HD session, and outcomes. The application of time-averaged volume status using measurements at some points between HD sessions or analyses using longitudinal data would be useful in overcoming these limitations. A large longitudinal study, including large sample size and both pre- and post-HD measurements, or longitudinal changes in volume status, is warranted to overcome these limitations.

In conclusion, this study demonstrates that high volume status may be associated with a decrease in muscle mass and physical performance regardless of inflammatory or nutritional status.

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.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of CHA Gumi Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK: research idea, study design, and data analysis and interpretation. JK: data acquisition, supervision or mentorship, and takes responsibility that this study has been reported honestly, accurately, transparently, and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JD: statistical analysis. SK and JD: wrote and revised the manuscript. 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.2022.754329/full#supplementary-material

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Non-linear Associations Between Visceral Adipose Tissue Distribution and Anthropometry-Based Estimates of Visceral Adiposity

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Scafoglieri A, Van den Broeck J, Cattrysse E, Bautmans I and Heymsfield SB (2022) Non-linear Associations Between Visceral Adipose Tissue Distribution and Anthropometry-Based Estimates of Visceral Adiposity. Front. Nutr. 9:825630. doi: 10.3389/fnut.2022.825630

Background: Recent evidence suggests that excess visceral adipose tissue (VAT) is associated with future loss of subcutaneous adipose tissue (SAT) and skeletal muscle (SM) with aging. In clinical settings (abdominal) circumferences are commonly used to estimate body composition (BC). We aimed to study the linearity of VAT distribution ratios (i.e., VAT/SAT ratio and VAT/SM ratio), waist-to-hip ratio (WHR) and waist circumference (WC) with age and the relationship of VAT distribution ratios with anthropometry (i.e., WHR and WC).

Materials and Methods: BC was determined using whole body magnetic resonance imaging in a large multi-ethnic group of 419 adults (42% white, 30% black, 15% Hispanic, 13% Asian, 1% other) with a BMI ranging from 15.9 to 40.8kg/m^2. Linear and non-linear regression analysis was used to examine the linearity of VAT distribution ratios and anthropometry from 18 to 88 years. The relation between VAT distribution ratios and anthropometry was assessed separately.

Results: In both sexes non-linear relationships were found between BC estimates and age, and between BC measures mutually. The ratios of VAT/SAT and VAT/SM showed quadratic relationships with age. VAT distribution ratios showed exponential or quadratic relationships with anthropometry with coefficients of determination ranging between 18 and 55%.

Conclusion: In both sexes, VAT distribution ratios showed curvilinear relationships with age and with anthropometry. Given the sex differences in VAT distribution ratios, WHR and WC represent different BC proportions in men and women. These results emphasize the challenge when interpreting changes in BC based upon linear extrapolations in clinical practice.

Keywords: visceral adipose tissue, subcutaneous adipose tissue, skeletal muscle, waist-to-hip ratio, waist circumference, nonlinearity

INTRODUCTION

The redistribution of tissues with aging, including the accumulation of ectopic fat in and around organs, has been related to the development of a variety of clinical disorders (1, 2). Aging induces changes in body composition (BC), such as an increase in visceral adipose tissue (VAT) and reduced muscle mass (3). Recently, it has been suggested that the accumulation of VAT precedes future loss of subcutaneous adipose tissue (SAT) and skeletal muscle (SM) (4–8). Understanding the intricate cross-talk between VAT and other tissue compartments may help clinicians in the screening for morbidity (9–12). Although still under investigation, the role of inflammation with aging has been brought forward as an important underlying mechanism in the development of cardiovascular and muscular dysfunction (13, 14). As a result, visceral adiposity and sarcopenic visceral obesity have been linked to adverse health outcomes (15–18) and negative survival (19–22).

Despite the accessibility to gold standard BC techniques in the context of potential life threatening health conditions such as diabetes or cancer, the need for simple, clinically applicable tools that can monitor changes in visceral and muscle tissue distribution over time remains topical. In clinical settings, the use of anthropometry-based markers of central obesity are widely accepted (23), but are not routinely obtained to determine disease risk (24–26). Although their ability to discriminate changes in VAT has previously been questioned (27, 28), there is a renewed interest in the use of waist circumference (WC) in the context of sarcopenic obesity (29, 30). Visceral adiposity and muscle mass change in opposite ways with aging (31), whereas anthropometry-based markers of central obesity gradually increase during lifespan (32–35). In order to advance our understanding of BC changes with aging (e.g., in the context of the operative definition of sarcopenic obesity) in clinical practice, the relation between VAT distribution ratios (i.e., VAT/SAT ratio, VAT/SM ratio), and anthropometry may be further explored (10, 36).

Previous studies investigating the relationship between VAT distribution, waist-to-hip (WHR) or WC have primarily considered a linear analytic approach (34). Investigating whether non-linear relations exist between different levels of organization in BC might help the interpretation of clinical results during screening for disease risk. Therefore we aimed to assess the linearity of VAT distribution ratios, WHR and WC to age in a multi-ethnic sample of healthy adults. Further, we assessed the linearity of VAT distribution ratios with WHR and WC in both sexes.

MATERIALS AND METHODS

Participants

Four hundred and nineteen healthy women (n = 224) and men (n = 195) varying in ethnicity and age were recruited amongst hospital employees of St. Luke's/Roosevelt Hospital (NY), students from Queen's University (ON) and the general public of Kingston and New York. The study was ethically approved by the respective institutional review boards. All participants signed a written informed consent form prior to enrollment. None of the participants reported medication intake known to affect body composition. The study procedures were in accordance with the World Medical Association's Declaration of Helsinki.

Magnetic Resonance Imaging Segmentation

The participants lay in prone position with their arms placed straight overhead in a 1.5 Tesla scanner (GE, Milwaukee, WI). MRI images were obtained with a T1-weighted, spin-echo sequence with a 210-ms repetition time and a 17-ms echo time. The details of the MRI protocol are described elsewhere (37, 38). A total of approximately 40 images with a slice thickness of 1 cm were acquired from each participant. The MRI data were analyzed using a semi-automatic software program for segmentation (Tomovision, Montreal, PQ). This software program allowed for the discrimination between adipose and muscle tissues based on their gray-level histogram output and a watershed algorithm for the selection of VAT. After segmentation a highly trained analyst specialized in tissular anatomy visually inspected and edited all images.

Body Composition Calculations

The volume of adipose and muscle tissue was calculated by multiplying the area in each image by the slice thickness. The volume of adipose and muscle tissue for the space between two consecutive slices was calculated with the use of a mathematical algorithm given elsewhere (38). The volume of tissues was converted to mass by multiplying the former by its assumed density. Densities of 0.92 g/cm^3 and 1.04 g/cm^3 were assumed for adipose tissue and muscle, respectively (39).

TABLE 1 | Characteristics of the participants.

	Women (n = 224)	Men (n = 195)
Age (years)	43.0 [32.0–56.0]	37.0 [28.0–47.0]†
Weight (kg)	64.9 [54.7–77.5]	80.0 ± 12.7†
Height (cm)	161.8 ± 7.2	176.9 ± 7.0†
BMI (kg/m^2)	24.5 [21.6–29.0]	25.1 [22.7–28.2]
WHR	0.78 [0.74–0.83]	0.87 [0.83–0.92]†
WC (cm)	78.0 [69.4–88.5]	87.6 ± 10.7†
AT (kg)	21.9 [16.4–32.6]	17.1 [12.4–23.2]†
VAT (g)	985.0 [535.0–2105.5]	1679.4 [770.0–3372.5]†
SAT (kg)	20.9 [15.6–31.2]	15.0 [10.8–19.9]†
SM (kg)	19.7 [17.5–21.9]	31.7 ± 5.5†
VAT/SAT	4.8 [3.2–7.8]	11.1 [6.7–18.3]†
VAT/SM	5.2 [2.9–10.1]	5.8 [2.4–10.2]*

Data are expressed as median [interquartile rage] or mean ± standard deviation, WC = waist circumference, WHR = waist-to-hip ratio, AT = total body adipose tissue, VAT = visceral adipose tissue, SAT = total body subcutaneous adipose tissue, SM = total body skeletal muscle mass, $^*p < 0.01$, $^\dagger p < 0.001$, body composition variables were corrected for age, weight and height (ANCOVA).

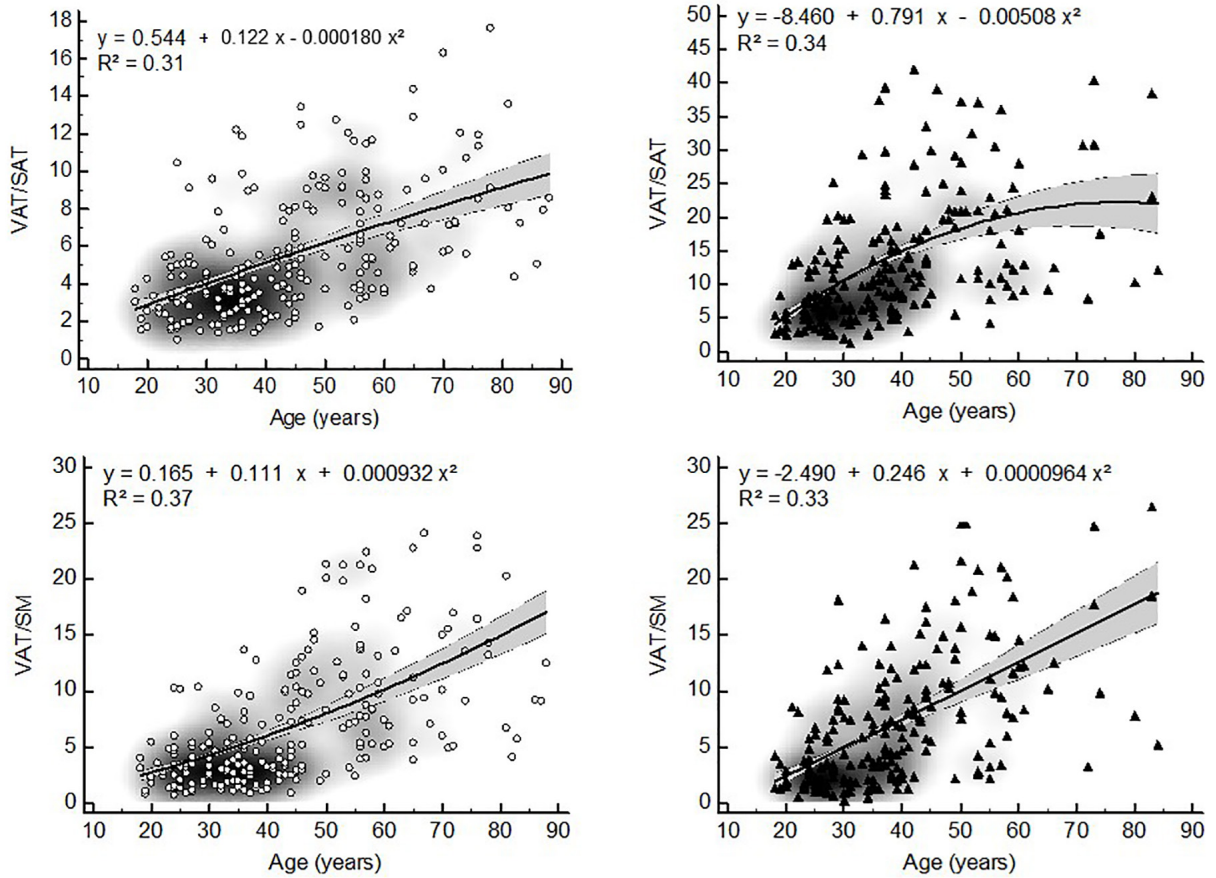

FIGURE 1 | Non-linear relationships between VAT distribution ratios and age (▲ = women, ▲ = men, VAT = visceral adipose tissue, WHR = waist-to-hip ratio, WC = waist circumference, gray zone represents 95% confidence interval).

Visceral Adipose Tissue Distribution Ratios

Visceral adipose tissue, total body SAT and total body SM were used to compute VAT distribution ratios. The ratio of VAT to SAT and the ratio of VAT to SM were used as metrics of VAT distribution.

Anthropometric Variables

Body mass was measured in minimal clothing on a digital scale to the closest 0.1 kg. Stature was recorded to the nearest 5 mm using a wall-mounted stadiometer according to standard procedures. Waist and hip circumference were taken to the nearest 1 mm with an anthropometric steel measuring tape. Waist circumference was measured midway between the iliac crest and lower rib border and hip circumference at the greatest protuberance of the gluteal muscles.

Statistical Analysis

Data were analyzed using MedCalc® Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium[1]). Data are expressed as group median [interquartile range] or mean ± standard deviation. Differences between women and men were tested for significance by unpaired *t*-tests or Mann-Whitney U tests, and for BC parameters by way of analysis of covariance (ANCOVA). Within each sex the linearity of the relation between VAT ratios, anthropometric variables and age was evaluated using linear and non-linear regression modeling based on least squares. An automatic weighted regression procedure was selected to correct for heteroscedasticity. The 0.05 level of significance was used for all data analyses.

[1]https://www.medcalc.org; 2021.

RESULTS

The characteristics of the participants can be found in **Table 1**. The ethnicity of the participants was equally divided between both sexes: Asian (13%), black (30%), Hispanic (15%), white (42%) and other (1%). Sixty-three percent of women were in the premenopausal period. After correction for age, height and weight, all BC variables were significantly different between sexes, except for BMI.

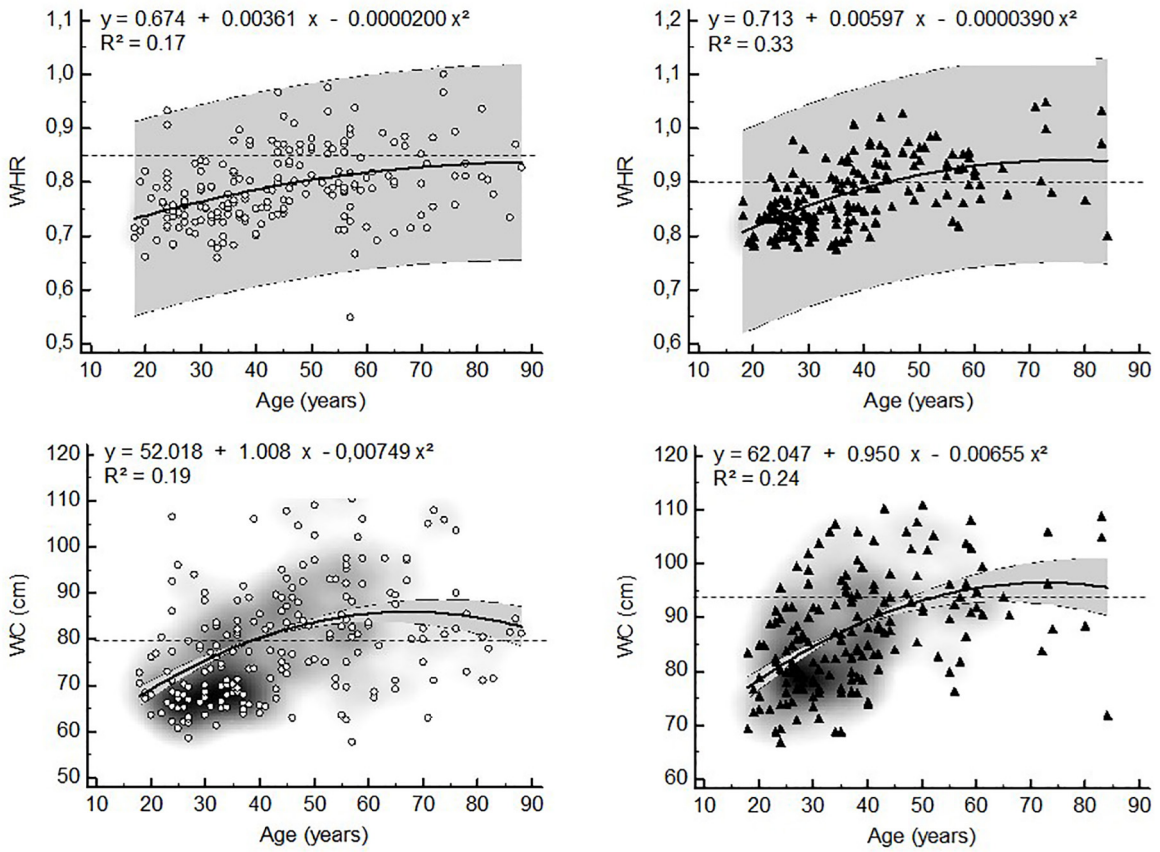

FIGURE 2 | Non-linear relationships between anthropometric estimates of visceral adiposity and age (▲ = women, ▲ = men, WHR = waist-to-hip ratio, WC = waist circumference, dashed lines represent WHO (25) cut points for increased cardiometabolic risk in whites, gray zone represents 95% confidence interval).

Relationships of Body Composition With Age

Visceral adipose tissue distribution ratios, WHR and WC were non-linearly related to age in both sexes. The models with the best fit showed that VAT distribution ratios were quadratically related to age in both sexes (**Figure 1**). Similarly WHR and WC showed quadratic relationships with age (**Figure 2**).

Relationships of Visceral Adipose Tissue Distribution Ratios With Waist Circumference and Waist-to-Hip Ratio

The VAT distribution ratios were non-linearly related to anthropometry-based markers of central obesity in both sexes (**Figures 3**, **4**). The ratio of VAT/SAT showed an exponential relationship with WHR (women: $R^2 = 0.25$; men: $R^2 = 0.47$) and a quadratic relationship with WC (women: $R^2 = 0.18$; $R^2 = 0.39$) (**Figure 3**). In both sexes, VAT/SM was exponentially related to WHR (women: $R^2 = 0.30$; men: $R^2 = 0.55$). The ratio of VAT/SM showed a quadratic relationship to WC (women: $R^2 = 0.44$; men: $R^2 = 0.55$) (**Figure 4**).

DISCUSSION

The main finding of this study is that visceral adipose tissue distribution is non-linearly related to age and to anthropometry-based estimates of visceral adiposity. Non-linear relationships between single BC compartments and age have been reported earlier and can be visualized by for example the Gaussian-like distribution for change in adiposity during life (32). Further, muscle and age show a curvilinear relationship due to the increasing rate in muscle loss with advanced aging (40). When used as indices, however, BC ratios (e.g., VAT/SAT) are often assumed to be linearly related to age or other BC components.

Although it has previously been reported that the ratio of VAT/SAT increases in a quasi-linear manner with age (34), we found quadratic relationships in both sexes. This can be explained by the fact that the slopes of the increase in VAT and SAT are significantly different between these compartments (**Figure 5**). Moreover, in old age the VAT compartment continues to increase slowly, while the SAT compartment starts to decrease slowly. Thus, the rate at which both BC compartments change differs considerably in time. As a result, the change in VAT/SAT distribution by age is more pronounced in middle adulthood than in old age.

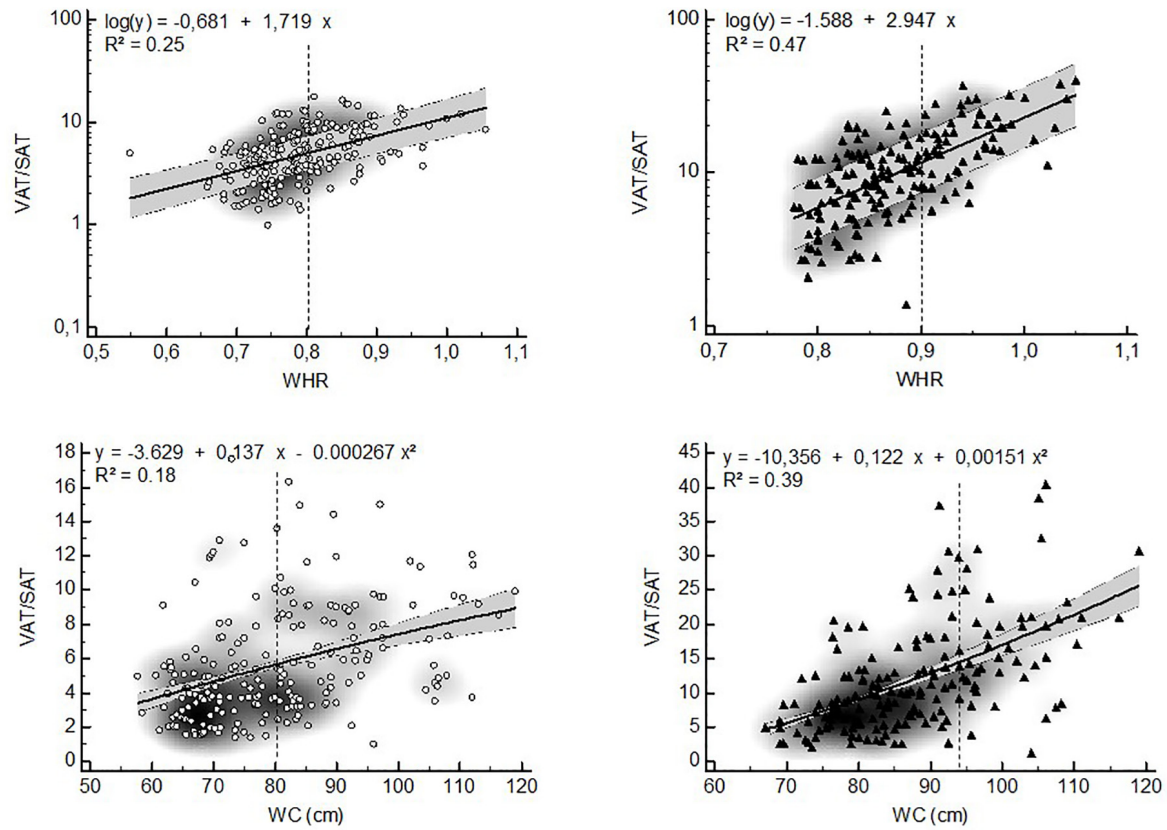

FIGURE 3 | Non-linear relationships between the VAT/SAT ratio and anthropometric estimates of visceral adiposity (▲ = women, ▲ = men, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, WHR = waist-to-hip ratio, WC = waist circumference, dashed lines represent WHO (25) cut points for increased cardiometabolic risk in whites, gray zone represents 95% confidence interval).

To the knowledge of the authors, no studies were found describing the relation of the VAT/SM ratio to age. Similar to VAT/SAT a quadratic relationship between VAT/SM and age was found in both sexes. Muscle mass starts to decrease at an age of about 50 years old and accelerates to decrease with advancing age. As a result, the change in VAT/SM shows a similar pattern to the change in VAT/SAT during life, although the former seems to change in a more pronounced way in old age. These results may therefore support the pathophysiological model whereby visceral adiposity accumulation in middle adulthood induces skeletal muscle insufficiency in old age, which in turn may possibly lead to the development of metabolic syndrome or sarcopenic visceral obesity (6, 41).

The changes in WHR and WC over time in the present study are in agreement with previous findings (32, 25). Waist and hip circumferences gradually increase with age until about 70 years old in both sexes. In older age (> 70 years) WHR and WC may further increase at slow rates of about 1-2% per decade in stable-weight subjects or decrease slowly in subjects losing weight (42–44). Since the changes in visceral adipose tissue distribution are more accentuated than the changes in circumferences with age, our results suggest that the latter may underestimate changes in visceral adipose tissue distribution especially in older persons.

Our results show that VAT distribution ratios are exponentially related to WHR and WC. This implies that BC proportions may change more rapidly than proxies of visceral adiposity, especially above the WHO cut points for increased risk. As a result, when used as surrogates for BC, WHR and WC should be corrected according to the risk category. For example, in men a WC of 120 cm corresponds to a VAT/SM ratio that is four times higher than the one at a waist of 90 cm (**Figure 3**). Of note, the VAT/SM ratio is similar across sexes below the cut points for increased metabolic risk based on WC. However, above these cut points the same increase in WC corresponds to a larger increase in VAT distribution in men compared to women, also highlighting the sex-specific differences in BC.

A recent pilot study showed that both VAT/SAT ratio and WHR correlate with pro-inflammatory cytokines in obese women, suggesting their potential role in the development of cardiometabolic dysfunction (45). Our study showed that VAT/SAT correlated best with WHR in both sexes. This is in contradiction with the findings of Tresignie et al. (46) and Bazzocchi et al. (47) who found no association between VAT/SAT ratio and WHR. Although our results are partially in agreement with those of Seidell et al. (48) who found a positive

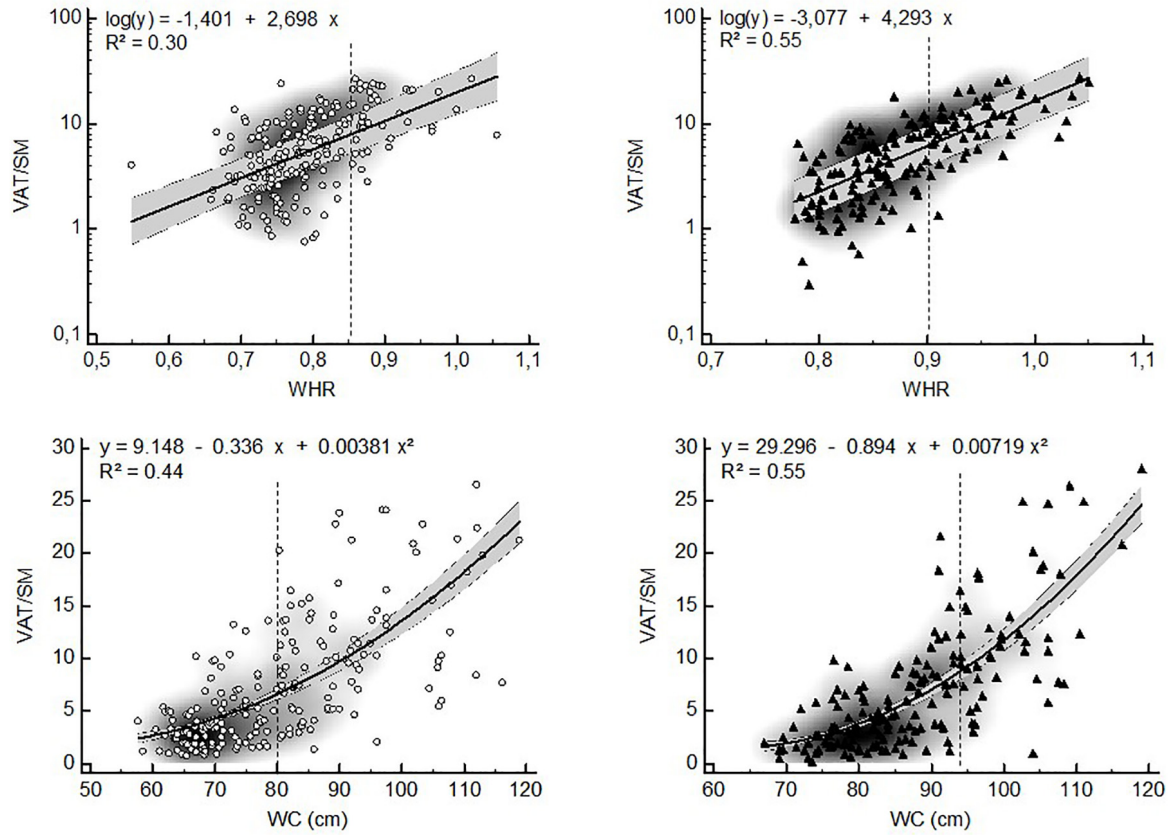

FIGURE 4 | Non-linear relationships between the VAT/SM ratio and anthropometric estimates of visceral adiposity (▲ = women, ▲ = men, VAT = visceral adipose tissue, SM = skeletal muscle, WHR = waist-to-hip ratio, WC = waist circumference, dashed lines represent WHO (25) cut points for increased cardiometabolic risk in whites, gray zone represents 95% confidence interval).

relation between VAT/SAT and WHR in women, the differences with other studies may be explained by the differences in the assessment of SAT. While it is common to calculate SAT from a medical imaging scan slice using CT or MRI, whole body SAT was used in the present study. Nevertheless, our findings may suggest that hip circumference better reflects whole body adiposity rather than regional (trunk) adiposity in healthy adults.

The VAT/SM ratio correlated best with WC in both sexes. Although most studies agree that redistribution of visceral adiposity occurs after menopause due to the absence of estrogens (49), Franklin et al. (50) found that menopause did not affect the relative abdominal adipose tissue distribution (VAT vs. SAT and VAT vs. muscle) or WC in their longitudinal study. As such, it is possible that the changes in body composition occurring directly after menopause may be captured by WC.

As pointed out, non-linear relationships between BC components have been described previously (32). Despite their different development rates during life, cross-sectional and longitudinal research in adult BC often assumes linear relationships between different levels of organization in BC. Since the interrelationship between these levels of organization might be more complex than usually assumed due to biological variation, their translation toward clinical practice remains challenging. This may be highlighted by the fact that the same amount of change in WC, may represent a variable change in BC components depending on age, sex and absolute quantities. In the field of BC there is a need to establish minimally important clinical differences (MICD), as it is unknown by which amount body components/proportions should change in order to make a difference to the patient. This approach may also help in the operational definition of BC related pathologies, such as cardiometabolic risk or sarcopenic visceral obesity. Future BC research should therefore also focus on determining the smallest change (at different levels of organization) in the treatment of individual patients with similar pathologies as MICD is depending on the BC components that are measured and their respective quantities. By doing so the cross-talk between different BC components in metabolic syndrome and/or sarcopenic visceral obesity may be further elucidated.

Limitations

There are a number of limitations to consider when interpreting our study results. First, WC was taken midway between the iliac crest and lower rib border. Since the absolute value of WC may differ up to 20% according to its measurement site, our results may only be valid for identical measurement protocols (51).

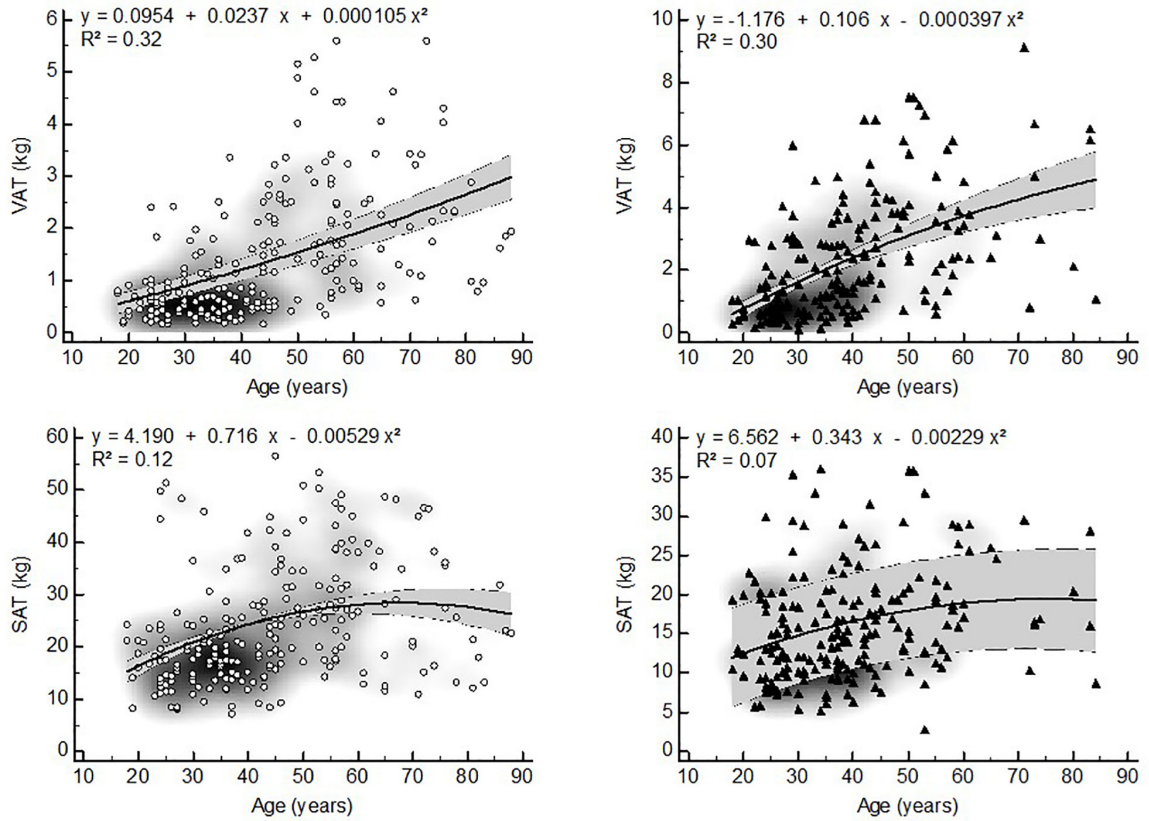

FIGURE 5 | Non-linear relationships between VAT, SAT and age (▲ = women, ▲ = men, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, gray zone represents 95% confidence interval).

Secondly, although we described the relation between BC and age, our data are cross-sectional. As longitudinal studies are more accurate in assessing age-related changes in BC than cross-sectional studies do, our results may underestimate the effects of aging on VAT distribution. Therefore longterm follow-up studies assessing VAT distribution changes over time are necessary to confirm our findings.

Finally, analysis of covariance (controlling for age, weight and height) showed that the VAT/SM ratio of Asian women is lower compared to that of white and black women. No other differences in body fat distribution or anthropometric estimates were apparent. Since the group of Asian women represents 13% of the total sample, we assumed that the impact of ethnic differences in body fat distribution may be rather small, albeit it cannot be excluded that the ethnic heterogeneity of our sample might have lowered the predictive accuracy of our regression models.

CONCLUSION

Visceral adipose tissue distribution is non-linearly related to age, WHR and WC. These relationships are curvilinear in nature and are influenced by age, sex and quantity. Since WHR and WC may represent different BC compartments, our results also emphasize the challenge when interpreting changes in BC based upon linear extrapolations.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by institutional review boards of St. Luke's/Roosevelt Hospital (NY) and Queen's University (ON). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS designed research (project conception, development of overall research plan, and study oversight), analyzed data or

performed statistical analysis, wrote the manuscript (major contribution), and had primary responsibility for final content. JV, EC, and IB had primary responsibility for final content. SH designed research (project conception, development of overall research plan, and study oversight), conducted research (hands-on conduct of the experiments and data collection), provided essential reagents or provided essential materials (contributed by providing constructs, databases, etc., necessary for research), and had primary responsibility for final content. All authors contributed to the article and approved the submitted version.

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The GLIM Criteria Represent a More Appropriate Tool for Nutritional Assessment in Patients With Crohn's Disease

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Background: The early recognition of malnutrition is essential for improving the prognosis of patients with Crohn's disease (CD). The Global Leadership Initiative on Malnutrition (GLIM) criteria represent a new consensus for the diagnosis of malnutrition but need to be validated in CD. The aims were to explore the related factors of malnutrition in CD and explore whether GLIM-positive patients who did not meet the Nutritional Risk Screening 2002 (NRS 2002) would benefit from nutritional treatment.

Methods: This study retrospectively enrolled patients with CD at the Gastroenterology Department of Xiangya Hospital Central South University between March 2020 and March 2021. After bioelectrical impedance analysis, all patients underwent nutritional screening and diagnosis using the NRS 2002 and GLIM criteria, respectively. Multivariable analysis was performed to evaluate risk factors related to malnutrition in patients with CD. A multivariable Cox hazard model was used to assess the association between nutritional therapy and prognostic outcomes.

Results: Of the 118 patients included, fifty were classified as having a high malnutrition risk according to the NRS 2002, while 76 were diagnosed with malnutrition by the GLIM criteria. Multivariate analysis showed that a high malnutrition risk was independently associated with the L4 phenotype [odds ratio (OR) (95% confidence interval (CI)) = 4.718 (1.108, 20.10), $p = 0.036$] and Crohn's Disease Activity Index (CDAI) [OR (95% CI) = 1.018 (1.007, 1.029), $p = 0.002$] based on the NRS 2002. The age at onset [OR (95% CI) = 0.828 (0.699, 0.980), $p = 0.028$] and CDAI [OR (95% CI) = 1.111 (1.034, 1.195), $p = 0.004$] were regarded as independent risk factors related to malnutrition, as determined by the GLIM criteria. Among 26 GLIM+/NRS− patients, significantly more patients who received nutritional support achieved 6-week remission than patients who did not (100 vs. 71.4%, $p < 0.05$). The 6-week remission risk in patients treated with nutrition therapy was more than 4-fold higher than those without nutritional therapy.

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Conclusion: The GLIM criteria could diagnose more malnourished patients with CD who are not positively screened by the NRS 2002, among whom nutritional support therapy would be beneficial for disease remission. The new criteria should be more appropriate for assessing the nutritional status of patients with CD.

Keywords: GLIM, NRS 2002, Crohn's disease, nutritional assessment, nutrition therapy

INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing, inflammatory disorder of the digestive tract that can lead to protein loss due to the presence of intestinal leaks. Several studies have reported that 20–40% of outpatients with CD present with specific nutrient deficiencies (1, 2).

Nutritional interventions may improve the outcomes of patients with CD, especially those with severe CD. Screening for and managing malnutrition by an appropriately trained multidisciplinary team is suggested in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (3). Previous researchers have demonstrated increased risks of venous thromboembolism (4), Non-elective surgery (5), longer hospital stays (5), and increased mortality in malnourished patients with CD (6). A meta-analysis revealed that the combination of enteral nutrition with biological agents was 2.4 times more effective in maintaining clinical remission than single treatments (7), suggesting that nutritional therapy plays an important role in the prognosis of patients with CD. However, nutritional treatment is not indicated in every patient, which requires nutritional screening and assessment. Therefore, early nutritional assessment is important in patients with CD.

The Nutritional Risk Screening 2002 (NRS 2002) is recommended by ESPEN guidelines for the nutritional screening in hospitalized patients (8). It classifies the severity of patients' disease in combination with the degree of malnutrition. Raslan et al. (9) assessed three nutritional screening tools for the measurement of nutritional risk, and the NRS 2002 was the best validated. Similarly, several studies have confirmed that the NRS 2002 was suitable for hospitalized Chinese patients (10, 11). Although the NRS 2002 saves time and is easy operation to apply, it is greatly affected by the patient's body mass index (BMI), which results in some malnourished patients with a normal BMI being easily missed. Therefore, there is still a need to find more suitable tools to screen and evaluate the nutritional status of patients with CD.

The Global Leadership Initiative on Malnutrition (GLIM) has been proposed to allow for comparisons and malnutrition diagnoses in regions that use a variety of assessment methods (12). The GLIM is a new diagnostic framework that focuses on building a global consensus around diagnostic criteria for malnutrition in adults (13, 14). Unlike the NRS 2002, the GLIM also assesses the muscle mass of patients. Recent studies have found that the patients with CD with a normal BMI may also suffer from sarcopenia (15). Their nutritional status may be easily overlooked by clinicians. The GLIM has not yet been applied in patients with various diseases, including CD, nor has its predictive value regarding outcomes in these patients. Further research is needed to determine the relevance of these criteria in clinical practice.

This study aims to explore the related factors of malnutrition in CD and to further evaluate whether GLIM-positive patients with CD who are not positively screened by the NRS 2002 can benefit from nutritional treatment.

METHODS

Patients Selection

This was a retrospective analysis of all adult patients who underwent assessment for CD at Central South University Xiangya Hospital between March 2020 and March 2021. Patients in the study population were newly diagnosed by a multidisciplinary inflammatory bowel disease (IBD) team composed of gastroenterologists, radiologists, pathologists, and dietitians, according to the guidelines established by the European Crohn's and Colitis Organization (ECCO) (16). Eligible subjects aged 18–60 years with a disease duration of 3 months, or longer were screened. No patients had indications for surgical intervention or other concomitant diseases. All eligible patients received infliximab (IFX) via intravenous administration. We excluded patients with anasarca, pregnant women, and those unable to undergo anthropometric measurements for various reasons. In addition, patients who were not treated according to the drug instructions (e.g., dose or frequency of drug administration), who were lost to follow-up or who had incomplete medical data available were excluded.

Data Collection

Clinical and demographic data were collected from the electronic records within the first 48 h of admission at the patients' bedside by the clinicians. The plasma C-reactive protein (CRP) level was used as a specific measure for the GLIM etiological criteria of inflammation, considering that all patients had an acute or chronic active disease burden (17). Additional nutritional therapy was collectively decided upon by the dietitians and clinicians, referring to the NRS 2002 results and the patient's decision.

For the nutritional assessment, trained dietitians evaluated the weight history, diet history, and body composition of the patients. Height and body weight were measured with a scale and stadiometer at the hospital. Eligible patients were required to be barefoot and wear as little clothing as possible (17). The weight loss of the patient within 6 months before hospitalization, was obtained to calculate the percentage of weight loss. A decrease in food and energy intake within 1 week before admission was

assessed. A tetrapolar multifrequency bioelectrical impedance analysis (BIA, Tanita, MC-180, Tokyo, Japan), set at a 50-kHz current frequency, was used to assess the body composition after voiding to determine the fat-free mass index (FFMI) (18). Before the measurement of BIA, patients were asked to refrain from performing any exercise, eating, and drinking fluids, including water, for at least 3 h, and were required to empty their bladder in time. During the measurements, patients were barefoot and remained stationary. A flow chart of the study process was shown in the **Figure 1**.

Definition

The primary outcome of this study was 6-week remission which was defined as a Crohn's Disease Activity Index (CDAI) <150 at week 6, without the need for any treatment escalation meaning any additional therapy or surgery during this time (19). The occurrence of CD-related surgical treatment and unplanned hospital admission within the first 6 weeks of IFX treatment were considered secondary endpoints.

In our study, if the patient's enteral nutrition intake exceeded 50% within 6 weeks, nutritional therapy was considered (20). By comparing the value of the actual total doses taken divided by the total doses prescribed during the 6-week period, we determined whether the actual intake was more than 50% (21). The actual total doses taken were calculated by the actual purchase records from the outpatient. The dietitians calculated the daily energy intake of each patient according to the ESPEN guidelines (22) and then converted it into the daily dose of enteral nutrition intake, which was the daily prescribed doses of the patient. The total doses prescribed during the 6 weeks were equal to the daily doses multiplied by the time (42 days). The guidelines require that the energy requirements of patients with CD are similar to those of the healthy population, about 25–30 kcal/kg/d (22). And 25 kcal/kg/d were selected in our hospital.

The Montreal classification was applied to define the location and behavior of the CD (23). The location was classified into four categories, including the terminal ileum (L1), colon (L2), ileocolon (L3) and upper gastrointestinal location (L4). The L4 phenotype was defined as involving esophagogastroduodenal, jejunal, or proximal ileal disease anatomically (24). The establishment of the diagnosis and classification was based on the findings of computed tomography enteroclysis, double-balloon enteroscopy and capsule endoscopy, as appropriate (3). The behavior of the disease included nonstricturing and nonpenetrating (B1), stricturing (B2), and penetrating (B3).

The GLIM includes three phenotypical criteria (weight loss, low BMI, and reduced muscle mass) and two etiological criteria (reduced food intake or absorption, and increased

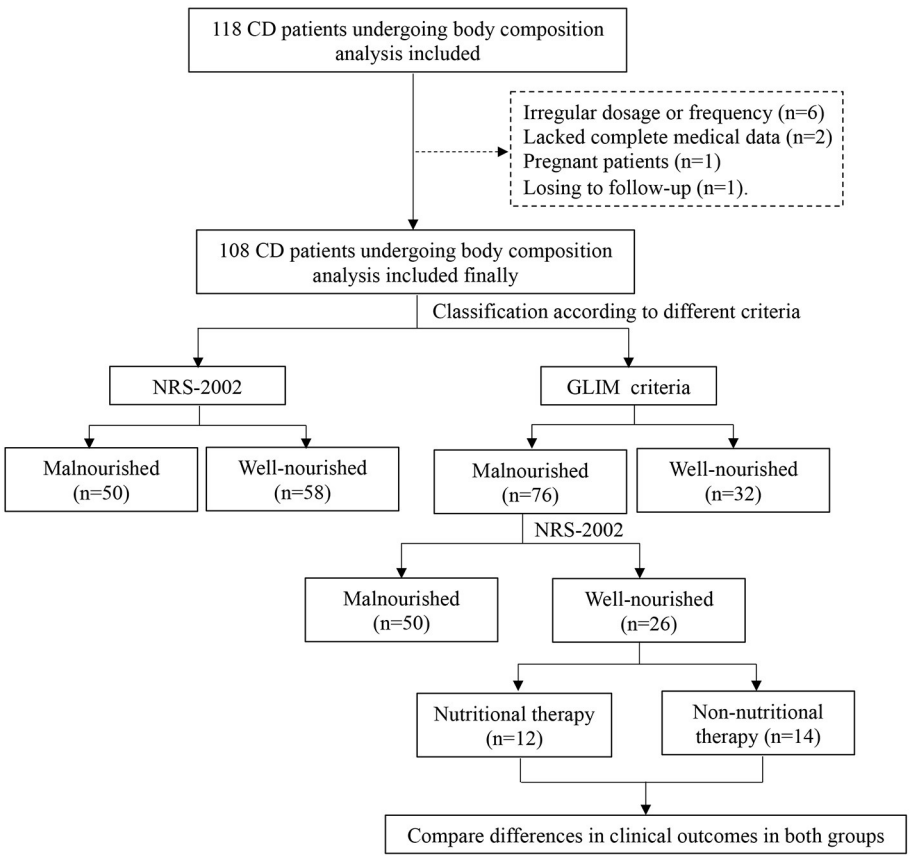

FIGURE 1 | A flow chart of the process of this study.

disease burden or inflammation). If a patient met at least one phenotypical criterion and one etiological criterion, malnutrition was diagnosed (12). Only one phenotypical criterion for this grade needed to be met to grade a patient's nutritional severity.

The details of the GLIM are as follows (12):

1. Weight loss: A nonvolitional weight loss of 5–10% within the past 6 months, or 10–20% beyond 6 months was defined as moderate malnutrition. A nonvolitional weight loss of >10% within the past 6 months, or >20% prior to the past 6 months was considered to indicate severe malnutrition.
2. BMI: The BMI cut-offs for malnutrition risk were <20 kg/m^2 if <70 years, and <22 kg/m^2 if ≥70 years, which was defined as moderate malnutrition. A BMI of <18.5 kg/m^2 for those aged <70 years, and <20 kg/m^2 for those aged ≥70 years, was considered to incadite severe malnutrition.
3. Reduced muscle mass: The parameter was assessed by the FFMI in this study. The FFMI cut-offs for malnutrition risk were <17 kg/m^2 for men and <15 kg/m^2 for women.
4. Reduced food intake or absorption: That was defined as an intake of 50% or less of energy requirements for >1 week, or any reduction for >2 weeks.
5. Increased disease burden or inflammation: Chronic or recurrent mild-to-moderate inflammation was likely to be associated with malignant disease or any disease that was considerded chronic or recurrent.

The NRS 2002 is based on the patient's nutritional status (including weight loss, BMI, and general condition or food intake) and disease severity (stress metabolism due to the degree of disease) (25). Each section was scored from 0 to 3 points. A total score ≥3 indicated a risk of malnutrition.

The GLIM+/NRS+ group included patients with CD who met the GLIM and NRS 2002, while the GLIM-/NRS− group inclued those who did not fulfill both sets of criteria. The patients who met the GLIM criteria but were negatively identified by the NRS 2002 were included in the GLIM+/NRS− group. And well-nourished patients with a high risk of malnutrition were included in the GLIM-/NRS+ group.

Statistical Analyses

Continuous variables, expressed as medians and interquartile ranges (IQR), were analyzed using Student's *t* test or nonparametric tests (the Mean-Whitney test) for those with a nonnormal distribution. Categorical variables were expressed as *n* (%). Differences between categorical variables were analyzed using the chi-square test and Fisher's exact probability test. Multivariable logistic regression analysis was performed to evaluate risk factors related to malnutrition in patients with CD. Variables with a p value <0.01 in the univariate analysis were included in the multivariate logistic regression analysis. However, BMI, weight, and FFMI were not considered in the multivariate analysis because they were closely related to the criteria mentioned in this study. A multivariable Cox proportional hazard model was used to assess the association of nutritional therapy with prognostic outcomes. All reported p values are two-tailed, and $p < 0.05$ indicated statistical significance. Analyses were performed with SPSS software (version 26.0).

RESULTS

Characteristics of the Study Population

There were 118 patients screened for inclusion in this study. Of these, six did not receive treatment according to the instructions, two lacked complete medical data, one patient was pregnant, and one patient was lost to follow-up. Finally, 108 patients with CD who received IFX were enrolled. Of those included, ∼69.4% were male, and three-fifths exhibited stenosis. They had a median BMI of 18.3 kg/m^2 (IQR, 16.6–20.2 kg/m^2). In addition, 54.6% of patients presented with perianal lesions. The baseline characteristics of the patients were presented in **Table 1**.

Analysis of Related Factors of High Malnutrition Risk in Patients With CD

A high malnutrition risk existed in 46.3% of participants at the time of admission according to the NRS 2002 criteria. The

TABLE 1 | Baseline characteristic of final cohort.

Variable	Final cohort (n = 108)
Male, No. (%)	75 (69.4%)
Height, median (IQR), cm	168.0 (160.0, 172.3)
Weight, median (IQR), kg	50.4 (45.3, 56.8)
BMI, median (IQR), kg/m^2	18.3 (16.6, 20.2)
FFMI, median (IQR), kg/m^2	15.6 (13.9, 16.9)
Age of onset, median (IQR), year	27.0 (17.0, 35.5)
Age at diagnosis, median (IQR), year	31.0 (19.0, 38.3)
Disease course, median (IQR), month	12.0 (3.0, 48.0)
Location, No. (%)	
L1	17 (15.7%)
L2	14 (12.9%)
L3	61 (56.5%)
L4	52 (48.1%)
Behavior, No. (%)	
B1	37 (34.3%)
B2	64 (59.3%)
B3	21(19.4%)
Perianal lesions, No. (%)	59 (54.6%)
Smoker, No. (%)	26 (24.1%)
Surgical history, No. (%)	33 (30.6%)
CDAI score, median (IQR)	188.3 (131.1, 250.6)
Serological examination	
White blood cell, median (IQR), 10^9/L	6.1 (4.4, 7.4)
NLR, median (IQR)	3.1 (2.2, 4.8)
LMR, median (IQR)	2.5 (1.7, 3.5)
PLR, median (IQR)	242.5 (177.9, 354.2)
Serum albumin, median (IQR), g/L	38.5 (33.8, 41.8)
CRP, median (IQR), mg/L	12.9 (4.2, 34.2)
Fibrinogen, median (IQR), g/L	4.1 (3.0, 4.9)

BMI, body mass index; FFMI, free fat mass index; CDAI, crohn's disease activity index score; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range.

patients at a high risk had lower FFMI levels ($p < 0.05$). Notably, these patients had a significant trend toward more involvement of the upper gastrointestinal tract ($p < 0.05$). In addition, the patients at a high risk tended to present with more severe inflammation, which manifested as higher CDAI scores and CRP levels ($p < 0.05$). On serological examinations, those in the high risk group had lower albumin levels, as well as LMR (lymphocyte-to-monocyte ratio) levels, and higher fibrinogen levels ($p < 0.05$).

The multivariate analysis with logistic regression showed that the L4 phenotype [odds ratio (OR) (95% confidence interval (CI)) = 4.718 (1.108, 20.10), $p = 0.036$] and an elevated CDAI [OR (95% CI) = 1.018 (1.007, 1.029), $p = 0.002$] were related factors of a the high malnutrition risk in CD. As presented in **Tables 2**, **3**, both groups were compared based on the NRS 2002.

Analysis of Related Factors of Malnutrition in Patients With CD

The study population was reclassified according to the GLIM criteria. In terms of weight, BMI, and FFMI ($p < 0.05$), the results were similar to those using the NRS 2002 as the classification criterion. Besides, malnourished patients were relatively younger at onset age than the well-nourished patients and exhibited higher CDAI and CRP levels ($p < 0.05$). No differences were found in other serological tests. In contrast, the age at onset [OR (95% CI) = 0.828 (0.699, 0.980), $p = 0.028$] and the CDAI score [OR (95% CI) = 1.111 (1.034, 1.195), $p = 0.004$] were regarded as the independent risk factors related to the nutritional status of patients according to the GLIM criteria. The detailed data were provided in **Tables 3**, **4**.

We found that ∼81.6% of the enrolled patients had severe malnutrition according to the GLIM criteria. The L4 phenotype

TABLE 2 | Comparison of patients according to the presence of malnutrition risk by NRS 2002.

Variable	NRS + group ($n = 50$)	NRS− group ($n = 58$)	P^*
Male, No. (%)	31 (62.0%)	44 (75.9%)	0.119
Height, median (IQR), cm	169.0 (158.0, 173.3)	168.0 (160.3, 170.0)	0.601
Weight, median (IQR), kg	46.0 (41.0, 49.8)	56.5 (53.2, 65.7)	0.000
BMI, median (IQR), kg/m^2	16.8 (15.5, 17.5)	20.3 (19.1, 22.6)	0.000
FFMI, median (IQR), kg/m^2	14.0 (13.0, 15.0)	16.8 (16.0, 18.0)	0.000
Age of onset, median (IQR), year	25.0 (17.0, 34.0)	30.0 (20.0, 40.5)	0.230
Age at diagnosis, median (IQR), year	28.0 (19.0, 37.0)	31.0 (20.5, 41.0)	0.389
Disease course, median (IQR), month	12.0 (3.0, 54.0)	12.0 (3.0, 30.0)	0.600
Location, No. (%)			
L1	10 (20.0%)	7 (12.1%)	0.259
L2	9 (18.0%)	5 (8.6%)	0.148
L3	26 (52.0%)	35 (60.3%)	0.383
L4	34 (68.0%)	18 (31.0%)	0.000
Behavior, No. (%)			
B1	18 (36.0%)	19 (32.8%)	0.723
B2	28 (56.0%)	36 (62.1%)	0.522
B3	7 (14.0%)	14 (24.1%)	0.184
Perianal lesions, No. (%)	29 (58.0%)	30 (51.7%)	0.514
Smoker, No. (%)	9 (18.0%)	17 (29.3%)	0.170
Surgical history, No. (%)	21(42.0%)	12 (20.7%)	0.017
CDAI score, median (IQR)	204.9 (165.0, 280.6)	154.0 (101.3, 192.0)	0.001
Serological examination			
White blood cell, median (IQR), 10^9/L	5.7 (4.4, 7.7)	6.3 (4.6, 7.3)	0.673
NLR, median (IQR)	3.4 (2.3, 4.9)	3.0 (2.0, 4.8)	0.455
LMR, median (IQR)	2.3 (1.6, 2.8)	2.8 (2.0, 4.3)	0.028
PLR, median (IQR)	262.5 (201.8, 373.3)	235.3 (136.2, 336.4)	0.246
Serum albumin, median (IQR), g/L	35.1 (31.7, 40.8)	39.9 (36.2, 43.7)	0.003
CRP, median (IQR), mg/L	19.0 (10.7, 70.8)	6.6 (3.4, 16.6)	0.002
Fibrinogen, median (IQR), g/L	4.5 (3.3, 5.4)	3.7 (2.6, 4.5)	0.034

NRS, Nutritional risk screening 2002; BMI, body mass index; FFMI, free fat mass index; CDAI, crohn's disease activity index score; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range.

**Mann-Whitney U test for continuous variables and chi-square for proportions.*

TABLE 3 | Multivariate analysis of factors related to high malnutrition risk by NRS 2002 and malnutrition by GLIM in patients with CD.

Criterion	Variable	Multivariate analysis	
		OR (95% CI)	*p*
NRS 2002	L4	4.718 (1.108, 20.10)	0.036
	CDAI score	1.018 (1.007, 1.029)	0.002
GLIM	Age of onset	0.828 (0.699, 0.980)	0.028
	CDAI score	1.111 (1.034, 1.195)	0.004

NRS 2002, Nutritional risk screening 2002; GLIM, global leadership initiative on malnutrition; CDAI, crohn's disease activity index score; OR, odds ratio; CI, confidence intervals.

was more common among patients with severe malnutrition than those with moderate dystrophy ($p = 0.031$). Similarly, they also had relatively higher CDAI scores and CRP levels ($p < 0.05$). The data were presented in the **Supplementary Table 1**.

Effect of Nutritional Therapy on Clinical Outcomes

In the study, patients were classified depending on whether they fulfilled the GLIM and NRS 2002 criteria. The results of classification were presented in **Table 5**. There were 50 patients with CD who were classified as having malnutrition with a high nutritional risk (i.e., GLIM+/NRS+ group), and 92% of them had received nutritional therapy. Thirty-two were well-nourished patients with a low nutritional risk (i.e., GLIM−/NRS− group), of whom only 9.4% received nutritional therapy. No well-nourished patients with a high nutritional risk (i.e., GLIM-/NRS+ group) were identified.

Additionally, of the 76 patients who met the GLIM criteria, twenty-six were negatively identified by the NRS 2002. These 26 patients were inclueded in the GLIM+/NRS− group. Of these patients, 46.2% (12/26) received nutritional therapy, while the remainder did not. **Table 6** showed the baseline data of the patients with CD treated with or without nutritional support. The clinical outcomes in these two groups were compared to further explore whether the patients missed by the NRS 2002 benefited from nutritional therapy. Among the GLIM+/NRS− patients, significantly more patients who received nutritional support achieved remission at 6-weeks than those who did not (100 vs. 71.4%, $p < 0.05$). The 6-week remission risk in patients with CD receiving nutritional therapy was more than 4-fold higher than in those without nutritional therapy after adjustment for age, gender, and disease activity [unadjusted hazard ratio (HR) (95% CI) = 2.610 (1.108, 6.147), $p = 0.028$]; adjusted HR (95% CI) = 4.251 (1.496, 12.08), $p = 0.007$). However, the rates of surgery and unplanned hospitalizations did not differ between the groups.

DISCUSSION

Malnutrition has been shown to affect the prognosis of patients with CD. Thus, it is important to have accurate criteria for the diagnosis of malnutrition in patients with CD. The current study demonstrated that disease phenotype, age of onset, and disease activity were associated with nutritional status in patients with CD treated with IFX. Furthermore, among GLIM+/NRS− patients, nutritional intervention could increase the likelihood of 6-week remission. The choice of the GLIM criteria appeared to be preferable in terms of clinical decision-making regarding nutritional therapy in patients with CD.

In this cohort, 70.4% of the patients with CD were diagnosed with malnutrition according to the GLIM criteria. This proportion appeared to be higher than those reported in recent studies, resulting in a prevalence of malnutrition ranging from 20 to 40% (26–28). This result may have been due to the lack of a consensus on the exact criteria for defining malnutrition in CD, which led to inconsistent and incomparable results. Furthermore, our cases were affected by active disease requiring biological treatment to reduce the offset, thus explaining the high proportion of patients with malnutrition.

This study showed that disease activity was associated with malnutrition regardless of whether the patients with CD were screened or diagnosed by the NRS 2002 or the GLIM criteria, respectively. Indeed, a severe inflammatory state not only disturbs intestinal barrier function, thereby increasing protein loss (29), but also contributes to the promotion of lipid oxidation and thermogenesis induced by the diet, which may lead to a difference in the basal metabolic rate between patients with both active and remissive CD, as shown in previous studies (30, 31).

Beyond that, we identified the L4 phenotype as an important factor of a high malnutrition risk when classified by the NRS 2002. The L4 phenotype was also observed more frequently in patients with severe malnutrition when classified according to the GLIM. Several studies have suggested that patients with the L4 phenotype have a worse prognosis than those with other phenotypes, which manifests as an increased risk for complications, surgery, and further hospitalization (24, 32–34). The small intestine is essential for the digestion and absorption of macro- and micronutrients (35). Intestinal cells impairment hampers the absorption of nutrients in the body (36, 37), which is sufficient to explain the predisposition of L4-phenotype patients to malnutrition.

Surprisingly, our findings also suggested that the age of onset similarly affected the nutritional status of patients. Previous literature have confirmed that younger patients predominantly have upper gastrointestinal involvement (38–40), and more frequently showed in progression to complicated disease states. Our study revealed a high cumulative proportion of patients with the L4 phenotype in the GLIM+ group, but the difference was not statistically significant. This result indicates that the classification of patients aged 18–60 years into age subgroups for further analysis might lead to more novel findings in subsequent studies if the sample size is sufficient. On the other hand, Xiao et al. (41) discovered that muscle mass was positively associated with age in adulthood and started to decrease from the fifth decade. Assessment of muscle mass is a routine item in the GLIM, which might increase the likelihood of young patients being assessed as positive according to that criterion. The studies mentioned above support the credibility of our results.

TABLE 4 | Comparison of patients according to the presence of malnutrition by GLIM criteria.

Variable	GLIM+ group ($n = 76$)	GLIM− group($n = 32$)	P^*
Male, No. (%)	50 (65.8%)	25 (78.1%)	0.204
Height, median (IQR), cm	169.0 (159.4, 173.0)	166.5 (160, 170)	0.465
Weight, median (IQR), kg	47.5 (44.1, 52.9)	58.8 (53.7, 66.4)	0.000
BMI, median (IQR), kg/m2	17.3 (15.8, 18.5)	21.5 (19.9, 23.7)	0.000
FFMI, median (IQR), kg/m2	14.5 (13.6, 16.0)	17.5 (17.0, 18.3)	0.000
Age of onset, median (IQR), year	25.0 (17.0, 31.8)	33.5 (24.8, 46.3)	0.017
Age at diagnosis, median (IQR), year	27.5 (19.5, 36.5)	35.0 (25.8, 47.0)	0.052
Disease course, median (IQR), month	12.0 (3.3, 57.0)	6.5 (1.8, 27.0)	0.198
Location, No. (%)			
L1	12 (15.8%)	5 (15.6%)	0.983
L2	13 (17.1%)	1 (3.1%)	0.097
L3	41 (53.9%)	20 (62.5%)	0.413
L4	40 (52.6%)	12 (37.5%)	0.151
Behavior, No. (%)			
B1	29 (38.2%)	8 (25.0%)	0.670
B2	44 (57.9%)	20 (62.5%)	0.656
B3	14 (18.4%)	7 (21.9%)	0.679
Perianal lesions, No. (%)	45 (59.2%)	14 (43.8%)	0.141
Smoker, No. (%)	14 (18.4%)	12 (37.5%)	0.061
Surgical history, No. (%)	24 (31.6%)	9 (28.1%)	0.722
CDAI score, median (IQR)	197.6 (152.4, 270.9)	141.7 (99.7, 198.0)	0.029
Serological examination			
White blood cell, median (IQR), 10^9/L	6.1 (4.4, 7.9)	5.9 (4.6, 7.0)	0.711
NLR, median (IQR)	3.2 (2.2, 4.9)	3.0 (1.9, 5.0)	0.640
LMR, median (IQR)	2.5 (1.7, 2.9)	2.8 (1.7, 4.6)	0.235
PLR, median (IQR)	245.6 (181.6, 340.5)	219.8 (133.4, 376.7)	0.784
Serum albumin, median (IQR), g/L	37.7 (33.4, 41.6)	38.9 (35.9, 43.6)	0.439
CRP, median (IQR), mg/L	17.2 (6.6, 47.8)	6.0 (3.6, 9.2)	0.005
Fibrinogen, median (IQR), g/L	4.4 (3.1, 5.2)	3.7 (2.7, 4.2)	0.063

GLIM, Global leadership initiative on malnutrition; BMI, body mass index; FFMI, free fat mass index; CDAI, crohn's disease activity index score; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range.

**Mann-Whitney U test for continuous variables and chi-square for proportions.*

In this study, the patients were divided into four groups using two sets of criteria to explore which patient population would benefit from nutritional intervention. Our study found mostly concordance in the decisions made by clinicians when the results of the two criteria were concordant. Additionally, no patients were assigned to the GLIM-/NRS+ group. This may be because the GLIM specifically assesses muscle mass in addition to most of the criteria in the NRS 2002. Therefore, the absence of such patients is justified.

However, nutritional therapy for GLIM+/NRS− patients is controversial. If different criteria are applied for clinical decision-making, clinicians will make different choices. Interestingly, our finding further indicated that nutritional therapy was effective in increasing the clinical remission rate among GLIM+/NRS− patients. Dietary therapy with exclusive enteral nutrition has been recommended as the first-line treatment for pediatric patients with CD (42), but the results of studies in adults have diverged. A recent review involing adults with CD evidenced that no differences in the ability of exclusive enteral nutrition and corticosteroids to induce remission (43). Consensus clinical guidelines in Japan recommend routine nutritional treatment for routine use (44). However, excessive nutritional therapy places an additional financial burden on patients and may not have a significant effect. Therefore, elucidating the appropriate indications for nutritional therapy is particularly critical.

TABLE 5 | Results of nutritional intervention in different groups of patients with CD.

Variable	Nutritional intervention	
	Yes	No
GLIM+/NRS+ group	46 (92.0%)	4 (8.0%)
GLIM+/NRS− group	12 (46.2%)	14 (53.8%)
GLIM−/NRS− group	3 (9.4%)	29 (90.6%)
GLIM−/NRS+ group	0 (0.0%)	0 (0.0%)

GLIM, Global leadership initiative on malnutrition; NRS, nutritional risk screening 2002.

TABLE 6 | Comparison of GLIM+/NRS− patients with or without nutritional therapy.

Variable	GLIM+/NRS− group ($n = 26$)	Nutritional therapy ($n = 12$)	Non-nutritional therapy ($n = 14$)	P^*
Male, No. (%)	18 (69.2%)	8 (66.7%)	10 (71.4%)	0.793
Height, median (IQR), cm	169.5(161.4, 174.3)	168.7 (162.4, 173.1)	169.9 (163.5, 172.8)	0.568
Weight, median (IQR), kg	47.5 (44.1, 52.9)	48.4 (45.2, 54.1)	47.4 (44.9, 53.6)	0.827
BMI, median (IQR), kg/m^2	17.3 (16.1, 18.1)	17.0 (16.4, 18.0)	16.8 (16.2, 17.9)	0.791
FFMI, median (IQR), kg/m^2	15.2 (14.4, 16.3)	15.1 (14.4, 16.2)	14.9 (14.5, 16.4)	0.773
Age of onset, median (IQR), year	26.0 (19.0, 32.5)	25.5 (19.0, 33.0)	26.0 (19.5, 33.5)	0.732
Age at diagnosis, median (IQR), year	28.0 (23.0, 38.5)	28.5 (23.0, 37.0)	28.0 (22.5, 38.5)	0.757
Disease course, median (IQR), month	12.0 (3.9, 48.5)	11.0 (4.5, 47.5)	12.2 (3.8, 48.0)	0.636
Location, No. (%)				
L1	4 (15.4%)	2 (16.7%)	2 (14.3%)	0.867
L2	5 (19.2%)	2 (16.7%)	3 (21.4%)	0.759
L3	14 (53.8%)	6 (50.0%)	8 (57.1%)	0.716
L4	12 (46.2%)	6 (50.0%)	6 (42.9%)	0.716
Behavior, No. (%)				
B1	10 (38.5%)	5 (41.7%)	5 (35.7%)	0.756
B2	14 (53.8%)	6 (50.0%)	8 (57.1%)	0.716
B3	5 (19.2%)	2 (16.7%)	3 (21.4%)	0.759
Perianal lesions, No. (%)	15 (57.7%)	7 (58.3%)	8 (57.1%)	0.951
Smoker, No. (%)	5 (19.2%)	2 (16.7%)	3 (21.4%)	0.759
Surgical history, No. (%)	8 (30.8%)	4 (33.3%)	4 (28.6%)	0.793
CDAI score, median (IQR)	198.1 (161.5, 264.8)	197.6 (165.7, 273.3)	200.1 (160.9, 252.6)	0.867
Endpoints				
6-week remission, No. (%)	21 (80.8%)	12 (100.0%)	10 (71.4%)	0.044
Surgery, No. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Unplanned hospitalization, No. (%)	1 (3.8%)	0 (0.0%)	1 (7.1%)	1.000
Serological examination				
White blood cell, median (IQR), 10^9/L	5.8 (4.1, 7.5)	6.1 (4.4, 7.3)	5.9 (4.1, 7.8)	0.986
NLR, median (IQR)	3.0 (2.1, 4.5)	3.1 (2.0, 4.3)	3.0 (2.0, 4.2)	0.849
LMR, median (IQR)	2.4 (1.5, 3.1)	2.2 (1.6, 3.1)	2.4 (1.4, 3.0)	0.109
PLR, median (IQR)	225.3 (185.7, 329.4)	231.4 (187.3, 316.4)	221.9 (191.1, 321.7)	0.639
Serum albumin, median (IQR), g/L	36.4 (32.5, 40.7)	36.8 (32.5, 41.3)	36.3 (34.1, 41.0)	0.094
CRP, median (IQR), mg/L	17.3 (6.4, 46.3)	16.9 (6.1, 45.2)	17.6 (6.5, 44.9)	0.783
Fibrinogen, median (IQR), g/L	4.2 (3.2, 5.4)	4.1 (3.2, 5.1)	4.3 (3.1, 5.7)	0.815

GLIM, Global leadership initiative on malnutrition; BMI, body mass index; FFMI, free fat mass index; CDAI, crohn's disease activity index score; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range.

**Mann-Whitney U test for continuous variables and chi-square for proportions.*

Previous evidence suggested that nutritional support improved the clinical outcomes of patients with NRS2002 scores higher than 3 (45). Our study considered that patients who were overlooked by the NRS 2002 would also benefit from nutritional therapy, further illustrating that the GLIM criteria may be more suitable in patients with CD. Additionally, the GLIM criteria consider muscle mass, which has been overlooked by the majority of criteria for evaluating malnutrition. A systematic review revealed that up to 60% of IBD patients exhibited skeletal muscle mass depletion (15), which correlated with the blockage of protein synthesis and absorption in patients (46). Interestingly, Adams et al. (47) reported that more than 40% of patients affected by sarcopenia presented with a normal BMI, and that up to 20% were overweight or obese, which were not identified as undernourished by traditional measures. Sarcopenia has been considered to be a meaningful marker of an adverse prognosis in patients with CD (48–50). Recent studies reported that moderate endurance and muscle training were beneficial for patients with quiescent or mildly active CD (51, 52), which may imply the potential impact of improved muscle status on disease activity to some extent. This potential effect is somewhat related to the assessment of muscle mass by the GLIM criteria. Therefore, screening for sarcopenia needs to be highlighted in the nutritional assessment of all patients with CD. The GLIM criteria allow the more timely screening of such potential patients than other tools.

Some limitations should be considered. Since this was a single-center study with a small sample size, subgroup analysis was restricted. Moreover, self-reporting rather than an in-depth historical diet assessment or a rigorous recording process was

used to assess food intake. Our study has a pragmatic design that reflects the reality in most clinical practices. In addition, the endpoints chosen for this study were short, and whether nutritional therapy can improve long-term outcomes in these patients requires continued reseach. The cost-benefit ratio of nutritional therapy in these patients will also be another focus of the follow-up studies.

In conclusion, an attempt was undertaken to evaluate the utilization of a new nutritional diagnostic framework in CD. The GLIM criteria could diagnose more malnourished patients with CD who are not screened by the NRS 2002, among whom nutritional support therapy would be beneficial for disease remission. Further prospective cohort studies are warranted to improve the better application of the GLIM for clinical guidance.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Xiangya Hospital of Central South University Ethics Committees, and each subject provided written, informed consent prior to study participation. 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

YL, ZP, DX, YP, and XL: study concept and design. ZP and DX: acquisition of data. YL, YP, and XL: analysis and interpretation of data. YL, ZP, and YP: statistical analysis. YL, YP, and XL: drafting of the manuscript. YL, ZP, DX, YP, and XL: critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript and including the authorship list.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.826028/full#supplementary-material

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Skeletal Muscle Mass Has Stronger Association With the Risk of Hyperuricemia Than Body Fat Mass in Obese Children and Adolescents

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Background: Hyperuricemia has been increasing among children with obesity in recent years. However, few studies in such a study group had explored the relationship between obesity-anthropometric indexes and hyperuricemia. This study aimed to examine the associations between hyperuricemia and different body components in children and adolescents with obesity, and further explore gender differences in these associations.

Methods: In this cross-sectional study, a total of 271 obese children and adolescents (153 boys and 118 girls) aged 6–17 years were recruited from Shanghai Xinhua Hospital. Data about basic information, anthropometric assessments, body composition, and laboratory tests of participants were collected.

Results: In this study, 73 boys (47.71%) and 57 girls (48.31%) were diagnosed to have hyperuricemia. The impacts of percentage of skeletal muscle (PSM) (OR = 1.221, $P < 0.001$) and skeletal muscle mass (SMM) (OR = 1.179, $P < 0.001$) on the risk of hyperuricemia was the largest, followed by hip circumference (HC) (OR = 1.109, $P < 0.001$), waist circumference (WC) (OR = 1.073, $P < 0.001$), and body fat mass (BFM) (OR = 1.056, $P < 0.05$) in whole sample, which was adjusted for age, gender and body mass index (BMI). After being stratified by gender, PSM (boys: OR = 1.309, $P < 0.001$) and SMM (boys: OR = 1.200, $P < 0.001$; girls: OR = 1.147, $P < 0.05$) were still the most predictors of hyperuricemia, followed by HC (boys: OR = 1.147, $P < 0.001$; girls: OR = 1.080, $P < 0.05$). WC showed a significant association with hyperuricemia only in boys (OR = 1.083, $P < 0.05$), while BFM showed no association with hyperuricemia in both gender groups after adjusting for age and BMI.

Conclusion: Our findings suggested that SMM was a stronger predictor of hyperuricemia than BFM in children and adolescents with obesity, especially in boys.

Keywords: hyperuricemia, obesity, skeletal muscle mass (SMM), body fat mass (BFM), children

INTRODUCTION

The pace of the obese population has been increasing dramatically and has becoming a major public health problem. According to WHO, the prevalence of overweight and obesity increased from 4% to 18% worldwide among children and adolescents aged 5–17 years (1). The latest national estimates in China between 2015 and 2019 showed that the prevalence of overweight and obesity was 11.1% and 7.9% among 6–17-year Chinese children and adolescents, respectively (2). Obesity in childhood also raises many health concerns, such as the non-alcoholic fatty liver disease (3), type 2 diabetes mellitus (4), and cardiovascular disease (4, 5), which cause a huge burden for the health-care services and the whole society.

Serum uric acid (UA) is a weak organic acid with low solubility in water, which could be endogenously synthesized or derived from purines and their derivatives in the diet. During childhood and adolescence period, the UA level of individuals can be regulated by renal and endocrine function, diet and energy expenditure, and metabolism (6). Hyperuricemia (HUA) is caused by the imbalance of serum UA and is often accompanied by obesity and metabolic syndrome (7). In adults, children, and adolescents, HUA was found to be closely related to cardiovascular risk (8), hypertension (9), and insulin resistance (10). Therefore, it is important to further clarify the mechanism of obesity and HUA, which could help to subsequently design intervention to lower the risk of HUA and HUA-related diseases in children with obesity.

Previous studies have shown that HUA was closely associated with obesity in adults and children (10–12), but few studies focused on the associations between specific body components or anthropometric indices and the risk of HUA among the obese population. It was reported that several obesity measurements, such as body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR), were identified as predictors of HUA or gout in adults (13). Another obesity determiner is the U shape association between body fat percentage and prevalence of HUA among adolescent athletes (14). Despite the BMI being an overall evaluation of an individual's body condition, it cannot differentiate the fat distribution from muscle mass, which means it cannot comprehensively assess the metabolic differences.

Some studies also suggested muscle mass and specific adiposity factors, such as WC, body fat mass (BFM), and visceral adipose tissue, were more clinically important predictors to evaluate an individual's obesity condition and metabolic syndrome than BMI (15, 16). However, the relationships of these factors with the risk of HUA in obese children and adolescents have not been examined simultaneously to date. Therefore, identifying the associations between specific body components or anthropometric indices and HUA are particularly important for better designing interventions or treatments to ameliorate obesity and UA levels in children with obesity.

This study aimed to examine the relationship between different anthropometric indices or body components [BMI, WC, hip circumference (HC), skeletal muscle mass (SMM), and BFM] and the risk of HUA, as well as the magnitude of their effects on HUA in obese children and adolescents. Since gender differences in serum UA levels were found physiologically higher in men than in women among the children age group (17, 18), we also verified if the gender differences exist among these associations in this study. To our knowledge, this is the first epidemiologic study examining whether different body components are independently associated with HUA in children and adolescents with obesity.

MATERIALS AND METHODS

Study Design and Participants

We conducted a retrospective study among children and adolescents, aged 6–17 years, with obesity who paid visits to the outpatient of Clinical Nutrition Department of Xinhua Hospital (Shanghai, China) from September 2012 to December 2019. The inclusion criteria for this study were the following: (a) children and adolescents aged 6–17 years old; (b) children and adolescents with obesity, wherein their BMI reached or exceeded the 95th percentile (P95) of children at the same age and gender according to the WHO standards (19). Participants with the following conditions were excluded: (a) currently receiving treatment for UA; (b) severe systemic, liver, and renal disorders; (c) taking medications that would impact obesity, such as stimulants or psychotropic drugs; (d) obesity caused by endocrine or genetic metabolic diseases. This study was approved by the Ethics Committee of Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University (No. XHEC-D-2021-177).

Data Collections

Anthropometric Assessments

Anthropometric measurements, including the height, body weight, WC, and HC of subjects were obtained. A vertical measuring board (Seca 264, Seca, Germany) was used to measure the height of subjects with no shoes at the floor level. Subjects were weighed on a hospital scale with indoor clothing and without shoes. WC and HC measurements were taken using a tape measure by a professional, and subjects were required to stand naturally and look straight ahead. For the WC measurement, the tape was wrapped around the waist horizontally from the midpoint between the bottom of the lower edge of the ribs and the highest point of the anterior superior iliac crest. As for measuring HC, the professional chose the most prominent part of the buttocks and then wrapped it horizontally around the buttocks using the same tape. All measurements were recorded to the nearest 0.1 cm or kg.

Body mass index, waist-to-hip ratio (WHR), and WHtR were calculated as follows: BMI was calculated as the weight in kilograms, divided by the height in meters squared (kg/m^2); the WHR was calculated by dividing the WC (cm) by the HC (cm); the WHtR was calculated by dividing the WC (cm) by the height (cm).

The BFM and SMM of subjects were measured using bioelectrical impedance analyses (BIA) by whole-body impedance (InBody720, Biospace Inc., South Korea). The percentage of body fat (PBF) and percentage of skeletal muscle (PSM) were calculated as follows: PBF (%) = (BFM in kg)/(weight in kg); PSM (%) = (SMM in kg)/(weight in kg).

Laboratory Test

Blood samples were collected in the morning by experienced nurses in Xinhua Hospital with the participants in fasting state and sent to the Clinical Laboratory Center for laboratory test of serum UA. The UA values (μmol/L) were detected by the uricase method using a Hitachi 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan).

The diagnosing criteria of HUA used the reference value for serum UA in Kubota's study (18) since UA values are highly dependent upon age. The reference cut-off levels are as follows: 5.5 mg/dL for 4–6 years, 5.9 mg/dL for 7–9 years, 6.1 mg/dL for 10–12 years in both genders, and 7 mg/dL (men) and 6.2 mg/dL (women) for 13–15 years. Furthermore, HUA was defined as above the mean UA values + 2 *SD* in each age group (16). For better comparison, we converted the UA values in this study with μmol/L to mg/dL using a conversion rate of 16.81 (1 mg/dl = 59.48 μ mol/L).

Statistical Analysis

Data were analyzed using SPSS version 22 software (SPSS Inc., Chicago, IL, United States). Continuous variables were presented as mean ± *SD* if they were normally distributed; otherwise, median (interquartile ranges) were used. For the categorical variables, they were presented as numbers and percentages (%). To compare the difference between gender, as well as between HUA and non-HUA, independent two-tailed *t*-tests were performed for normally distributed continuous data, Wilcoxon signed-rank tests were performed for non-normally distributed continuous variables, while the Chi-square test was used for categorical variables. Binary logistic regression models were used to evaluate the impacts of different body component variables on the risk of HUA. Model 1 was an unadjusted regression; Model 2 was a regression with age and sex-adjusted; Model 3 was a regression with BMI adjusted building upon model 2. All *P*-values were calculated by two-sided tests, and the significance level for each test was set at $P < 0.05$.

RESULTS

Characteristics of Subjects

A total of 271 subjects consisted of 153 boys and 118 girls were included in this study. The total mean age was 9.79 years (10.87 years in boys and 9.29 years in girls). As presented in **Table 1**, boys had higher height, weight, WC, HC, BMI, WHR, and WHtR in comparison with girls ($P < 0.05$). Also, boys had higher SMM and UA levels than girls ($P < 0.05$) when it comes to body components and serum UA level, while no significant differences between PSM, BFM, and HUA were found between the two groups.

Comparison Between Hyperuricemia and Non-Hyperuricemia Groups

In 271 subjects, 130 of them (47.97%) were diagnosed to be HUA, among which 73 were boys while 57 were girls. As shown in **Table 2**, the average age in the HUA group was lower than non-HUA group, but other variables, including height, weight, BMI, SMM, PSM, BFM, WC, and HC, in the HUA group were all higher in HUA than non-HUA group ($P < 0.05$). In addition, the WHR was lower while the WHtR was higher in the HUA group than in the non-HUA group, wherein this significance only existed in boys with obesity ($P < 0.05$).

Body Component Parameters and the Risk of Hyperuricemia

Binary logistic regression results were shown in **Table 3**, BMI [odds ratio (OR) = 1.198, 95% CI: 1.119–1.283], SMM, PSM, BFM, WC, and HC were positively associated with the risk of HUA after adjusting for age and gender among all participants (Model 2, all $P < 0.001$). Also, the SMM, PSM, BFM, WC, and HC were still positively associated with the risk of HUA after adjusting for age, gender and BMI in Model 3 (all $P < 0.05$), with the extent of PSM (OR = 1.221, 95% CI: 1.103, 1.352) > SMM (OR = 1.179, 95% CI: 1.099–1.264) > HC (OR = 1.109, 95% CI: 1.059 to 1.161) > WC (OR = 1.073, 95% CI: 1.026–1.121) > BFM (OR = 1.056, 95% CI: 1.004–1.11).

Among specific gender groups, the regression results showed that the BMI (OR = 1.121, 95% CI: 1.107–1.326), SMM, PSM, BFM, WC, and HC were all positively associated with the risk of HUA after adjusting for age in boys with obesity (all $P < 0.001$). On the other hand, after adjusting for both age and BMI in Model 3, the PSM (OR = 1.309, 95% CI: 1.129, 1.519), SMM (OR = 1.2, 95% CI: 1.097–1.313), HC (OR = 1.147, 95% CI: 1.067–1.233), and WC (OR = 1.083, 95% CI: 1.017–1.154) were still positively associated with the risk of HUA in boys ($P < 0.05$).

Among girls with obesity, the BMI (OR = 1.117, 95% CI: 1.057–1.31), SMM, BFM, WC, and HC were also positively associated with the risk of HUA after adjusting for age (all $P < 0.01$). Whereas after adjusting for age and BMI, only the SMM (OR = 1.147, 95% CI: 1.018–1.293) and HC (OR = 1.08, 95% CI: 1.016–1.148) were still positively associated with the risk of HUA ($P < 0.05$) in the said study group.

DISCUSSION

In this study, we found that the risk of HUA was positively associated with PSM, SMM, HC, WC, and BFM in obese children after controlling for age, gender, and BMI. When we analyzed the data by gender, we found that PSM, SMM, HC, and WC were still positively associated with HUA in boys, while SMM and HC were also still positively associated with HUA in girls, after adjusting for age and BMI. Specifically, the impacts of SMM (especially PSM) and HC on the risk of HUA were the largest and second in children and adolescents with obesity, in which these results were consistent after stratified by gender.

Obesity, generally defined as abnormal or excessive fat accumulation, has an adverse impact on an individual's health (20). In our study, the proportion of obese children with HUA was 47.97% (47.71% in boys and 48.31% in girls), which was higher than some previous studies which documented around 20% HUA among obese children (7). BMI increased overall 19.8% risk of HUA in children and adolescents with obesity in this study. The relationship between obesity and HUA was interactional and

TABLE 1 | General characteristics of study subjects.

	Total (*n* = 271)	Boys (*n* = 153)	Girls (*n* = 118)	*P**
Age (y)	9.79 (8.07, 11.72)	10.87 ± 2.68	9.29 ± 2.15	<0.001
Height (m)	1.44 (1.35, 1.58)	1.50 ± 0.15	1.40 ± 0.13	0.029
Weight (kg)	53.25 (43.42,71.32)	62.70 (48.60, 79.15)	46.51 (37.30, 55.74)	<0.001
BMI (kg/m^2)	26.28 (23.51, 29.57)	27.70 (24.68, 31.11)	24.32 (21.64, 27.07)	<0.001
WC (cm)	86.00 (78.00, 96.00)	92.55 ± 12.63	80.69 ± 11.66	<0.001
HC (cm)	91.35 (83.77, 91.35)	96.93 ± 12.58	88.57 ± 11.99	<0.001
WHR	0.93 (0.89, 0.93)	0.95 ± 0.06	0.91 ± 0.07	<0.001
WHtR	0.59 ± 0.05	0.61 ± 0.05	0.57 ± 0.05	<0.001
SMM (kg)	16.80 (13.70, 22.92)	19.60 (15.35, 25.05)	14.95 (11.84, 18.49)	<0.001
PSM (%)	31.75 (30.00, 33.56)	31.84 (30.20, 33.61)	31.63 (29.68, 33.56)	0.474
BFM (kg)	25.45 (20.30, 31.77)	26.47 ± 9.58	26.70 ± 7.74	0.829
PBF (%)	39.40 (36.17, 43.20)	39.70 (37.25, 43.15)	38.70 (35.20, 43.27)	0.065
UA (mg/dl)	5.90 (5.03, 7.10)	6.30 ± 1.74	5.90 ± 1.25	0.036
HUA [*n* (%)]	130 (47.97)	73 (47.71)	57 (48.31)	0.923

**P-values were the results of the difference between boys and girls with obesity. BMI, body mass index; SMM, skeletal muscle mass; PSM, Percentage of skeletal muscle; BFM, body fat mass; PBF, Percentage of body fat; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; UA, uric acid; HUA, hyperuricemia.*

TABLE 2 | Comparison of the body characteristics between hyperuricemia (HUA) and non-HUA groups.

	Total (*N* = 271)		Boys (*N* = 153)		Girls (*N* = 118)	
	HUA	Non-HUA	HUA	Non-HUA	HUA	Non-HUA
N (%)	130 (47.97)	141 (52.03)	73 (47.71)	80 (52.29)	57 (48.31)	61 (51.69)
Age (y)	9.50 (8.02, 11.35)	9.98 (8.14, 12.11)*	10.42 (8.49, 11.86)	11.29 (9.21, 13.18)†	9.23 (7.95, 10.33)	9.34 (7.85, 10.00)
Height (m)	1.52 ± 0.14	1.40 ± 0.13*	1.58 ± 0.14	1.43 ± 0.13†	1.45 ± 0.12	1.35 ± 0.13‡
Weight (kg)	63.80 (50.07, 81.42)	48.31 (39.88, 60.22)*	76.78 (61.95, 92.00)	56.41 (46.18, 63.88)†	55.72 (42.34, 65.42)	44.89 (34.77, 51.80)‡
BMI (kg/m^2)	27.56 (24.05, 31.28)	25.18 (22.74, 27.70)*	30.07 (26.06, 33.02)	26.82 (24.51, 28.78)†	25.94 (22.52, 28.49)	23.45 (20.80, 25.86)‡
SMM (kg)	19.89 (15.77, 26.20)	15.12 (12.10, 19.27)*	25.69 (18.15, 33.20)	17.61 (14.18, 21.15)†	17.49 (13.81, 20.10)	14.29 (10.97, 16.78)‡
PSM (%)	31.97 (30.17)	31.65 (29.84, 33.35) *	32.41 (30.36, 34.84)	31.58 (29.73, 32.83)†	31.56 (29.57, 33.47)	31.75 (29.90, 33.66)
BFM (kg)	28.13 (23.37, 34.72)	22.68 (18.40, 28.07) *	30.03 (22.35, 37.35)	23.23 (17.60, 27.93)†	28.93 (24.55, 33.50)	24.63 (10.01, 28.45)‡
PBF (%)	39.35 (36.30, 43.46)	39.41 (35.77, 42.90)	39.20 (36.40, 43.10)	40.30 (37.90, 43.50)	39.73 ± 6.24	37.69 ± 5.85
WC (cm)	91.73 ± 13.83	83.38 ± 11.98*	97.61 ± 12.84	87.94 ± 10.57†	84.22 ± 11.25	77.41 ± 11.15‡
HC (cm)	98.35 ± 13.11	88.63 ± 11.01*	102.65 ± 12.87	91.71 ± 9.82†	92.85 ± 11.34	84.58 ± 11.27‡
WHR	0.93 ± 0.06	0.94 ± 0.07	0.95 ± 0.05	0.96 ± 0.08†	0.91 ± 0.07	0.92 ± 0.05
WHtR	0.60 ± 0.05	0.59 ± 0.05	0.62 ± 0.05	0.61 ± 0.05†	0.58 ± 0.06	0.57 ± 0.06

**Significance between HUA and Non-HUA groups in all subjects ($P < 0.05$).*
†Significance between HUA and Non-HUA groups in boys with obesity ($P < 0.05$).
‡Significance between HUA and Non-HUA groups in girls with obesity ($P < 0.05$).
BMI, body mass index; SMM, skeletal muscle mass; PSM, Percentage of skeletal muscle; BFM, body fat mass; PBF, Percentage of body fat; WC, waist circumference; HC, hip circumference, WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

complex. For example, HUA can be caused by obesity through increasing the UA synthesis and inhibiting its excretion, but it consequently results to a high level of UA which also develops obesity by accelerating body fat accumulation (especially visceral fat) (21). BMI reflects the overall body condition and is shown to be positively associated with UA levels or the risk of HUA in previous studies (22, 23). In their discussions about this finding, the author usually mentioned the effects of SMM and BFM on UA, since BMI could provide potential estimates of body fat and muscle. Thus, these findings and discussions also prompted us to further clarify the associations between HUA and some body components, such as BFM and SMM.

Our findings showed that BFM and WC were positively associated with the risk of HUA in children with obesity after adjusting for age, gender, and BMI, which was consistent with some previous studies (24, 25). The mechanisms of the association between BFM and HUA have been discussed and about the following aspects: firstly, with the accumulation of body fat, the levels of several inflammation markers, such as interleukin (IL)-6 and tumor necrosis factor α (TNF-α), have increased, which were positively related to serum UA levels in the obese population (26, 27). In addition, excess adipose tissue would be a major contributor to insulin resistance (IR) or peripheral IR (28, 29), which has been confirmed as a key risk of HUA, since IR was found to have an ability to (1) directly affect the reabsorption of UA and ultimately lead to HUA (30) or (2) indirectly promote lipolysis to increase the production of nicotinamide adenine dinucleotide phosphate (an important

TABLE 3 | Logistic regression about body component parameters and the risk of HUA.

	Model 1	Model 2	Model 3
Variables	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Whole sample			
BMI	1.140 (1.077, 1.207)***	1.198 (1.119, 1.283)***	/
SMM	1.138 (1.088, 1.190)***	1.192 (1.127, 1.261)***	1.179 (1.099, 1.264)***
PSM	1.106 (1.024, 1.194)*	1.097 (1.015, 1.185)*	1.221 (1.103, 1.352)***
BFM	1.089 (1.053, 1.126)***	1.097 (1.060, 1.136)***	1.056 (1.004, 1.110)*
WC	1.052 (1.030, 1.073)***	1.082 (1.054, 1.111)***	1.073 (1.026, 1.121)***
HC	1.069 (1.045, 1.094)***	1.095 (1.064, 1.126)***	1.109 (1.059, 1.161)***
Boys			
BMI	1.191 (1.094, 1.297)***	1.121 (1.107, 1.326)***	/
SMM	1.174 (1.103, 1.249)***	1.196 (1.116, 1.282)***	1.200 (1.097, 1.313)***
PSM	1.221 (1.084, 1.376)**	1.211 (1.073, 1.367)**	1.309 (1.129, 1.519)***
BFM	1.090 (1.046, 1.136)***	1.105 (1.057, 1.156)***	1.091 (0.979, 1.216)
WC	1.073 (1.040, 1.108)***	1.086 (1.050, 1.124)***	1.083 (1.017, 1.154)*
HC	1.091 (1.054, 1.130)***	1.104 (1.063, 1.148)***	1.147 (1.067, 1.233)***
Girls			
BMI	1.140 (1.037, 1.254)***	1.177 (1.057, 1.310)***	/
SMM	1.156 (1.060, 1.262)***	1.182 (1.073, 1.302)***	1.147 (1.018, 1.293)*
PSM	1.020 (0.934, 1.114)	1.018 (0.932, 1.113)	1.133 (0.971, 1.321)
BFM	1.086 (1.026, 1.149)**	1.088 (1.027, 1.151)**	1.055 (0.987, 1.127)
WC	1.059 (1.020, 1.099)**	1.075 (1.031, 1.122)***	1.060 (0.993, 1.132)
HC	1.069 (1.030, 1.110)***	1.081 (1.037, 1.128)***	1.080 (1.016, 1.148)*

Model 1: Crude model.
Model 2: Whole sample: adjusted for age and gender; boys and girls: adjusted for age.
Model 3: Whole sample: adjusted for age, gender, and BMI; boys and girls: adjusted for age and BMI.
**P < 0.05, **P < 0.01, ***P < 0.001. OR, odds ratio; CI, confidence interval; BMI, body mass index; SMM, skeletal muscle mass; PSM, Percentage of skeletal muscle; BFM, body fat mass; PBF, Percentage of body fat; WC, waist circumference; HC, hip circumference.*

source of UA) (31, 32). In this study, increased WC led to a higher risk of HUA than the BFM in total participants. However, stratified analysis by gender revealed that only WC still showed positively related to HUA in boys, and neither BFM nor WC showed an association with HUA in girls with obesity. As a marker of abdominal fat accumulation and visceral adiposity in children and adolescents (33, 34), WC showed a greater association with HUA than BFM (a relative overall indicator of body fat). Such findings further elucidated visceral adipose accumulation was more closely related to HUA in children and adolescents, especially in boys, which was consistent with previous studies in adults (23–25). For children and adolescents with simple obesity, it was less noticed that the muscle mass also increased greatly as a fat mass did (35). The first study about the association between muscle mass and UA levels in 823 Brazilian children and adolescents, which was published in 2020 and showed that a positive association between muscle mass and UA levels in both boys and girls, and muscle mass has explained the respective 43 and 7.7% of the variability of UA levels (17). In our study, it was worth noting that PSM and SMM were found to be the most powerful predictors to the risk of HUA in children with obesity, even after being stratified by gender. As known, UA is an end-product of purine catabolism from endogenous (nucleic acids and internal pool of purines, accounting for approximately 80%) and exogenous sources (dietary purines, accounting for 20%) (36) of the body. Furthermore, muscle mass is considered as the largest source of purine in the body (37). During the process of its growth, muscle cells release plenty of nucleic acids and purines due to the depletion of themselves or metabolism of adenosine triphosphate, which in turn results in increased production of UA (36, 38). Therefore, it is reasonable to attribute an increased serum UA level to an increase in muscle mass. On the other hand, increased levels of intramyocellular lipids could also elevate IR from skeletal muscles (39). Thus, we speculated that the IR may be further enhanced and the risk of HUA might increase among children with high muscle and high fat, which needs more empirical evidence to support. In our study, PSM and SMM were the most powerful predictor of the risk of HUA, followed by HC, and these magnitudes were greater in boys than in girls, which also suggested the role of muscle played in the increase of UA levels. In this study, the PSM, SMM, and HC were significantly greater in boys than girls. Larger HC usually reflects higher muscle mass (40, 41), which might be a potential explanation of the magnitude of HC on HUA higher than WC. These findings also provided evidence about the effect of muscle on HUA.

To our best knowledge, this is the first study that showed that SMM had a stronger association with the risk of HUA than BFM in obese children. Considering the gender differences in body compositions and UA levels, boys and girls were also stratified

in the analysis to ensure the reliability of the results. The results among these study groups were mostly consistent to support muscle as the most powerful predictor to HUA in our study, especially in boys with greater muscle mass. However, several limitations also need to be mentioned. Firstly, due to the cross-sectional design of this study, our findings cannot be regarded as causal inferences between different body components and UA levels or HUA. Longitudinal studies are warranted to examine their relationships. Secondly, as mentioned before, part of UA can also be catabolically produced from exogenous sources (e.g., dietary purines), which means lack of dietary data about protein intake and analysis about its impact on HUA could also be a limitation. Despite this, the body composition can be regarded as an indirect reflection of dietary and nutritional status.

To be concluded, not only the BMI, higher PSM, SMM, HC, WC, and BFM were found to be positively associated with a higher risk of HUA independently in children with obesity. PSM and SMM were stronger predictors than BFM in HUA in obese children, especially in boys. The relationships between obesity and HUA are more complex than it appears. Thus, in clinical practice, more attention should be paid only not to BFM and BMI, but also to muscle mass in children with obesity (especially in boys) in order to reduce the risk of HUA and potential related metabolic diseases. Moreover, further prospective studies are warranted to clarify whether a reduction of muscle mass and fat mass could reduce UA levels, and the underlying mechanisms of the relationships among them still need more evidence.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethic Committee of Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LX, YN, PM, WC, and YF conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. XZ, XLZ, YN, and QT designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Comparing SARC-CalF With SARC-F for Screening Sarcopenia in Adults With Type 2 Diabetes Mellitus

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Background: The prevalence of sarcopenia is high in older people with type 2 diabetes mellitus (T2DM) and is now considered a critical problem in the healthcare sector. However, the preferred screening tool for identifying sarcopenia remains unknown. Thus, the aim of this study was to ensure that the diagnostic values of the SARC-F (strength, assisting with walking, rising from a chair, climbing stairs, and falling) and SARC-CalF (SARC and calf circumference) scales were compared with five reference diagnostic criteria for sarcopenia.

Methods: This was a cross-sectional study. Patients diagnosed with diabetes were treated at the First Affiliated Hospital of Wenzhou Medical University. Appendicular skeletal muscle mass, muscle strength, and physical performance were assessed using dual-energy X-ray absorptiometry, handgrip strength, and gait speed assessment. Five diagnostic criteria for sarcopenia (Asian Working Group for Sarcopenia, International Working Group on Sarcopenia, Foundation for the National Institutes of Health, Sarcopenia Project, Society on Sarcopenia Cachexia and Wasting Disorders, and European Working Group on Sarcopenia in Older People criteria) were utilized. Sensitivity and specificity analyses were performed on the SARC-CalF and SARC-F scales. The diagnostic precision of both instruments was determined using the receiver-operating characteristic (ROC) curves and area under the ROC curves (AUC).

Results: This study included 689 subjects (459 men and 230 women) with a mean age of 58.1 ± 13.2 years. In accordance with the five reference diagnostic parameters, the prevalence of sarcopenia was between 4.5 and 19.2%. In addition, the range of sensitivity of SARC-F and SARC-CalF ranged from 61.4 to 67.4 and 82.6 to 91.8%, respectively. Concurrently, the specificity ranged from 63.1 to 67.3 and 51.5 to 61.2%, respectively. Overall, AUC values for SARC-CalF were higher than those for SARC-F, regardless of the diagnostic standard, sex, or age.

Conclusion: The results of this study suggest that SARC-CalF significantly enhances the sensitivity and overall diagnosis of SARC-F. SARC-CalF appears to be an optimal screening tool for sarcopenia in adults with T2DM.

Keywords: type 2 diabetes mellitus, sarcopenia, SARC-F, SARC-CalF, specificity, sensitivity, diagnostic criteria

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INTRODUCTION

According to the definition, sarcopenia is the accelerated loss of skeletal muscle mass, muscle strength, and physical performance associated with old age or chronic disease. Additionally, it can result in negative effects, including falls, fractures, functional disability, enhanced hospital admission rates, reduced quality of life, and even death (1).

Diabetes mellitus (DM) is a metabolic disease that lasts for a lifetime. As individuals suffering from diabetes live longer, sarcopenia has recently been considered as one of the chronic complications of DM (1). Various studies have indicated that the prevalence of sarcopenia in people with type 2 DM (T2DM) is 1.56–3 times higher than in non-diabetics. In addition, sarcopenia is significantly related to glycemic control and the duration of diabetes (2–4). Therefore, early detection, early diagnosis, and treatment of sarcopenia in patients with diabetes are highly crucial. Current guidelines allow certain devices to evaluate body composition, such as computed tomography (CT), dual-energy X-ray absorption (DXA), and bioimpedance analysis (BIA). Nevertheless, since these devices are inaccessible in many clinical situations, a short and easy-to-use sarcopenia screening tool is needed (5, 6).

Several screening tools are available for screening sarcopenia. For instance, SARC-F, which was developed in 2013, is the most extensively applied questionnaire in several populations. SARC-F focuses on strength, assisting with walking, rising from a chair, climbing stairs, and falling (7). However, it has shown high specificity but low sensitivity, which may affect its potential as a screening tool for identifying individuals with sarcopenia (8–10). Recently, another tool for screening sarcopenia, known as SARC-CalF (SARC and calf circumference) (11), was reported by Sliva et al. This integrates SARC-F and calf circumference (CC), which greatly enhances the sensitivity and accuracy of SARC-F diagnosis. Yang et al. equally discovered similar results in Chinese elderly people (12, 13). Nevertheless, these results should be applied to diverse populations.

From what is known, people with diabetes have a higher tendency for developing sarcopenia; however, few studies have examined the diagnostic performance of SARC-F and SARC-CalF in predicting sarcopenia in adults with T2DM. Therefore, a cross-sectional study was performed to fill this gap.

MATERIALS AND METHODS

Study Design and Population

In this study, a diagnostic accuracy study was conducted. From June 2020 to June 2021, a total of 689 inpatients with T2DM according to the criteria of the American Diabetes Association of the Endocrinology Department were recruited at the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China. The exclusion criteria were as follows: (1) age ≤18 years; (2) type 1 DM (T1DM) and other types of DM; (3) malignant tumor; (4) autoimmune diseases; (5) taking medications that may affect body composition; (6) long-term bedridden patients; (7) severe disease of the heart, liver, or kidneys; and (8) inability to communicate with investigators.

All participants provided written informed consent. The study protocol utilized in this study was approved through the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Assessment of Sarcopenia With SARC-F and SARC-CalF

To evaluate sarcopenia risk, the SARC-F and SARC-CalF scales were implemented (**Supplementary Table 1**).

The SARC-F Scale

The SARC-F scale examines five domains: (1) strength; (2) walking assistance; (3) rising from a chair; (4) climbing stairs; and (5) falls, with scores ranging between 0 and 2. A score of ≥4 points implies positive sarcopenia screening (7).

The SARC-CalF Scales

The SARC-CalF scale contains six objects; the first five objects have the same score as SARC-F, and the sixth object is CC. In accordance with the 2019 Asian Working Group for Sarcopenia (AWGS) criteria, CC thresholds were 34 and 33 cm for men and women, respectively. If the score is above the cut-off value, CC is scored as 0; if it is below the cut-off value, the score is 10. A score of ≥11 points indicates a positive screening for sarcopenia (5).

TABLE 1 | Five diagnostic criteria for sarcopenia and the cut-off applied.

Diagnosis definition	Muscle mass	Muscle strength	Physical performance
EWGSOP1	SMI ≤ 7.26 kg/m^2 for men SMI ≤ 5.50 kg/m^2 for women	HGS < 30 kg for men HGS < 20 kg for women	GS < 0.8 m/s for both gender
AWGS2019	SMI < 7 kg/m^2 for men SMI < 5.4 kg/m^2 for women	HGS < 28 kg for men HGS < 18 kg for women	GS < 1 m/s for both gender
IWGS	SMI ≤ 7.2 kg/m^2 for men SMI ≤ 5.67 kg/m^2 for women		GS < 1 m/s for both gender
SCWD	SMI ≤ 6.81 kg/m^2 for men SMI ≤ 5.18 kg/m^2 for women		GS < 1 m/s for both gender
FNIH	ASM/BMI < 0.789 for men ASM/BMI < 0.512 for women	HGS < 26 kg for men HGS < 16 kg for women	

SMI, skeletal muscle mass index; ASM, appendicular skeletal muscle mass; BMI, body mass index; HGS, handgrip strength; GS, gait speed.

TABLE 2 | Characteristics of the study population.

Variable	Overall (n = 689)	Men (n = 459)	Women (n = 230)	p-Value[a]
Age (years)*	58.1 ± 13.2	56.4 ± 13.6	61.7 ± 11.7	<0.001
Diabetes duration (years)‡	10.0 (3.0, 15.0)	9.0 (2.0, 15.0)	10.0 (5.0, 15.3)	0.028
HbA1c (%)*	9.6 ± 2.4	9.7 ± 2.4	9.3 ± 2.3	0.040
FPG (mmol/L)*	8.9 ± 3.0	8.8 ± 2.8	9.1 ± 3.2	0.206
2hPG (mmol/L)*	19.8 ± 4.7	19.5 ± 4.6	20.4 ± 4.9	0.023
HOMA-IR‡	2.7 (1.7, 4.6)	2.5 (1.5, 3.9)	3.4 (1.9, 5.2)	<0.001
ALT (U/L)‡	21.0 (14.0, 32.0)	23.0 (15.0, 35.0)	17.0 (13.0, 25.0)	<0.001
AST (U/L)‡	21.0 (17.0, 29.0)	22.0 (17.0, 31.0)	20.0 (17.0, 26.0)	0.007
eGFR*	95.2 ± 28.3	96.4 ± 30.6	92.8 ± 22.8	0.112
BMI (kg/m^2)*	23.6 ± 3.4	23.7 ± 3.4	23.2 ± 3.3	0.076
WC (cm)*	90.1 ± 9.4	90.5 ± 9.4	89.3 ± 9.4	0.133
CC (cm)*	33.7 ± 3.6	34.3 ± 3.6	32.5 ± 3.2	<0.001
HGS (kg)*	29.0 ± 10.5	33.6 ± 9.3	19.8 ± 5.8	<0.001
GS (m/s)*	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	<0.001
ASM (kg)*	20.0 ± 4.4	22.1 ± 3.6	15.9 ± 2.6	<0.001
SMI (kg/m^2)*	7.3 ± 1.2	7.7 ± 1.1	6.4 ± 0.9	<0.001
ASM/BMI*	0.9 ± 0.2	0.9 ± 0.1	0.7 ± 0.1	<0.001
SARC-F‡	0 (0, 1)	0 (0, 1)	1 (0, 1)	<0.001
SARC-CalF‡	3 (0, 10)	1 (0, 10)	10 (1, 11)	<0.001
SARC-F classification†				0.070
Non-sarcopenia	658 (95.5%)	443 (96.5%)	215 (93.5%)	
Sarcopenia	31 (4.5%)	16 (3.5%)	15 (6.5%)	
SARC-CalF classification†				<0.001
Non-sarcopenia	549 (79.7%)	386 (84.1%)	163 (70.9%)	
Sarcopenia	140 (20.3%)	73 (15.9%)	67 (29.1%)	
EWGSOP1 classification†				0.063
Non-sarcopenia	557 (80.8%)	362 (78.9%)	195 (84.8%)	
Sarcopenia	132 (19.2%)	97 (21.1%)	35 (15.2%)	
AWGS2019 classification†				0.243
Non-sarcopenia	574 (83.3%)	377 (82.1%)	197 (85.7%)	
Sarcopenia	115 (16.7%)	82 (17.9%)	33 (14.3%)	
IWGS classification†				0.732
Non-sarcopenia	607 (88.1%)	403 (87.8%)	204 (88.7%)	
Sarcopenia	82 (11.9%)	56 (12.2%)	26 (11.3%)	
SCWD classification†				0.092
Non-sarcopenia	640 (92.9%)	421 (91.7%)	219 (95.2%)	
Sarcopenia	49 (7.1%)	38 (8.3%)	11 (4.8%)	
FNIH classification†				0.090
Non-sarcopenia	658 (95.5%)	434 (94.6%)	224 (97.4%)	
Sarcopenia	31 (4.5%)	25 (5.4%)	6 (2.6%)	

HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; 2hPG, 2-h postprandial glucose; HOMA-IR, homeostasis model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; BMI, body mass index; WC, waist circumference; CC, calf circumference; HGS, handgrip strength; GS, gait speed; ASM, appendicular skeletal muscle mass; SMI, skeletal muscle mass index. The Student's t-test and Mann–Whitney U-test were used for the continuous variables and the X^2 test for the categorical variables.

**Data are presented as the means (SDs).*

†*Data are presented as numbers (percentages).*

‡*Data are presented as medians (interquartile ranges).*

[a]*The p-value represents the difference between the male and female groups.*

TABLE 3 | Sensitivity, specificity, PPV, NPV, +LR, and −LR analyses and ROC curves for SARC-F and SARC-CalF validation against varying sarcopenia criteria.

	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR	AUC	p-Value[a]
EWGSOP1 classification								
SARC-F	61.4 (52.5–69.7)	67.3 (63.3–71.2)	30.8 (27.1–34.8)	88.0 (85.5–90.2)	1.9 (1.6–2.2)	0.6 (0.5–0.7)	0.67 (0.63–0.71)	<0.001
SARC-CalF	82.6 (75.0–88.6)	61.2 (57.0–65.3)	33.5 (30.7–36.5)	93.7 (91.0–95.6)	2.1 (1.9–2.4)	0.3 (0.2–0.4)	0.79 (0.76–0.82)	
AWGS2019 classification								
SARC-F	62.6 (53.1–71.5)	66.7 (62.7–70.6)	27.4 (23.9–31.2)	89.9 (87.5–91.9)	1.9 (1.6–2.3)	0.6 (0.4–0.7)	0.67 (0.63–0.70)	<0.001
SARC-CalF	87.8 (80.4–93.2)	61.0 (56.8–65.0)	31.1 (28.5–33.8)	96.2 (93.8–97.6)	2.3 (2.0–2.5)	0.2 (0.1–0.3)	0.81 (0.78–0.84)	
IWGS classification								
SARC-F	63.4 (52.0–73.8)	65.2 (61.3–69.0)	19.8 (16.8–23.1)	93.0 (90.8–94.6)	1.8 (1.5–2.2)	0.6 (0.4–0.8)	0.65 (0.62–0.69)	<0.001
SARC-CalF	89.0 (80.2–94.9)	54.9 (50.8–58.9)	21.0 (19.2–23.0)	97.4 (95.2–98.6)	2.0 (1.8–2.2)	0.2 (0.1–0.4)	0.78 (0.74–0.81)	
SCWD classification								
SARC-F	67.4 (52.5–80.1)	64.1 (60.2–67.8)	12.5 (10.3–15.2)	96.2 (94.5–97.5)	1.9 (1.5–2.3)	0.5 (0.3–0.8)	0.66 (0.62–0.69)	<0.001
SARC-CalF	91.8 (80.4–97.7)	52.8 (48.9–56.7)	13.0 (11.7–14.3)	98.8 (97.1–99.5)	2.0 (1.7–2.2)	0.2 (0.1–0.4)	0.78 (0.75–0.81)	
FNIH classification								
SARC-F	64.5 (45.4–80.8)	63.1 (59.3–66.8)	7.6 (5.9–9.8)	97.4 (95.9–98.4)	1.8 (1.3–2.3)	0.6 (0.3–0.9)	0.65 (0.62–0.69)	0.052
SARC-CalF	90.3 (74.2–98.0)	51.5 (47.6–55.4)	8.1 (7.1–9.2)	99.1 (97.5–99.7)	1.9 (1.6–2.1)	0.2 (0.1–0.6)	0.74 (0.71–0.77)	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; AUC, area under the ROC curves. Values within parentheses represent the 95% confidential intervals.

[a]*The p-value represents the difference between the SARC-F and SARC-CalF groups.*

Assessment of Muscle Mass, Muscle Strength, and Physical Performance

Muscle mass was assessed in each subject using DXA (Model: Prodigy Primo – 81013GA series; software 11.40.004, GE Healthcare United States, Shanghai Agent in Asia, Shanghai,

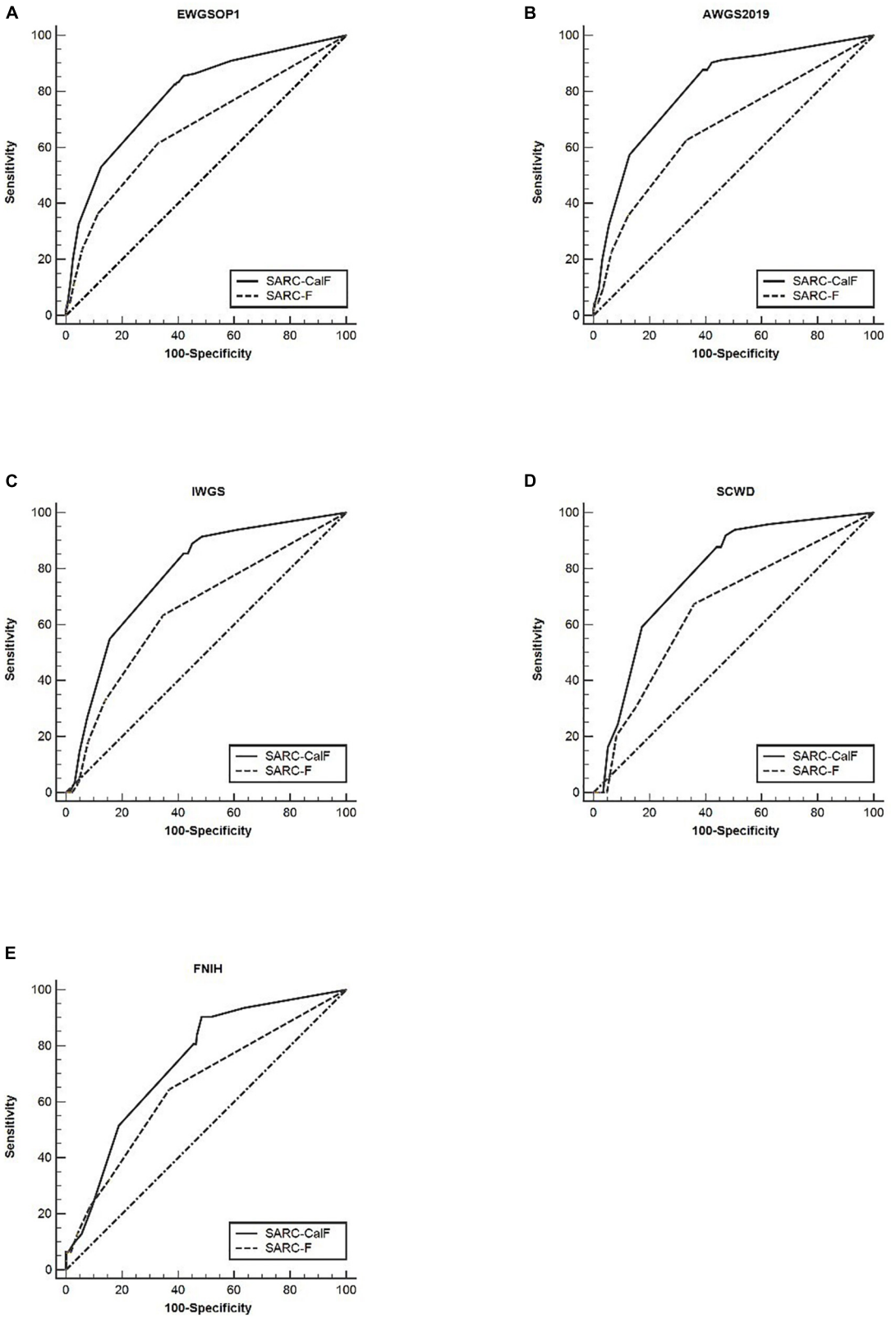

FIGURE 1 | The ROC curves of SARC-F and SARC-CalF were contrasted with various reference standards in the entire population studied: **(A)** sarcopenia according to the EWGSOP1 criteria; **(B)** sarcopenia according to AWGS2019 criteria; **(C)** sarcopenia according to IWGS criteria; **(D)** sarcopenia according to SCWD criteria; and **(E)** sarcopenia according to FNIH criteria.

China) by experienced radiologists. Before analysis, subjects were required to wear only a hospital gown and all-metal accessories. Scanning was taken while lying down. The software provides estimates of appendicular skeletal muscle mass (ASM), which is the sum of lean body mass in the upper and lower extremities (14). The ASM assessed and calculated the skeletal muscle mass index (SMI) and ASM/body mass index (BMI). The SMI was computed from the equation: $\text{SMI (kg/m}^2) = \frac{\text{ASM (kg)}}{\text{height}^2\ (\text{m}^2)}$.

The muscle strength was assessed on the basis of handgrip strength (HGS) using a portable electronic dynamometer with a precision of 0.1 kg (Brand: CAMRY, Model: TH-01, XIANGSHAN, Zhongshan, and Guangdong Province, China). Subjects who performed the HGS test were seated with their arms at their sides and with their elbows flexed at 90°. They squeezed the handle as hard as they could. Trained surveyors assessed the subject's dominant hand three times, with an interval of 1 min between each measurement. All measured values were recorded, and the maximum value was taken as the muscle strength.

In this study, the gait speed (GS) test was measured as the physical performance. The subjects were instructed to walk a distance of 6 m in their normal gait. If necessary, canes and walkers were adopted. The GS measurement was performed twice with an accuracy of 0.1 m, and the mean value was recorded.

Clinical Data

General clinical data, such as demographic information, duration of illness, medical history, and medication status, were collected.

All anthropometric measurements were performed in the morning without eating before the assessments. Trained nurses measured weight (kg) and height (m) at 0.1 kg and 0.1 cm, respectively. BMI (kg/m^2) was computed as the body weight divided by the square of the height. The CC was assessed when the subjects were in a sitting position with their soles touching the surfaces of the floor, with the assumption that the widest circumference of the right calf was being used. Waist circumference (WC) was measured midway between the top of the hip bone and the lower rib when the subjects were in a standing position. The measurement of the CC and WC required the use of anthropometric tape. CC and WC must be accurate to the nearest 0.1 cm.

After fasting overnight, blood samples were taken from the antecubital vein and centrifuged at 5000 rpm for 20 min. Before conducting the assay, the plasma was stored in freezing tubes at −80°C. Biochemical indices include glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), 2-h postprandial glucose (2hPG), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). All items were assessed in the Biochemistry Department of the First Affiliated Hospital of Wenzhou Medical University. Insulin resistance (IR) was assessed through the application of the homeostasis model (HOMA-IR), which was computed as follows: $\text{HOMA}-\text{IR} = \frac{\text{FPG(mmol/l)}*\text{FINS(mIU/l)}}{22.5}$ (15), and the estimated glomerular filtration rate (eGFR) was computed in accordance with the CKD-EPI formula (16).

Assessment of Sarcopenia Using Different Diagnostic Criteria

The five diagnostic classifications are utilized for screening sarcopenia: (1) the European Working Group on Sarcopenia in Older People (EWGSOP) (17); (2) the AWGS (5); (3) the International Working Group on Sarcopenia (IWGS) (18); (4) the Society on Sarcopenia Cachexia and Wasting Disorders (SCWD) (19); and (5) the Foundation for the National Institutes of Health (FNHI) Sarcopenia Project (20).

TABLE 4 | Sensitivity, specificity, PPV, NPV, +LR, and −LR analyses and ROC curves for SARC-F and SARC-CalF validation against different sarcopenia criteria in men.

	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR	AUC	*p*-Value[a]
EWGSOP1 classification								
SARC-F	55.7 (45.2–65.8)	74.9 (70.1–79.2)	37.2 (31.6–43.3)	86.3 (83.3–88.8)	2.2 (1.7–2.8)	0.6 (0.5–0.7)	0.67 (0.62–0.71)	<0.001
SARC-CalF	83.5 (74.6–90.3)	64.6 (59.5–69.6)	38.8 (34.9–42.7)	93.6 (90.3–95.8)	2.4 (2.0–2.8)	0.3 (0.2–0.4)	0.80 (0.76–0.84)	
AWGS2019 classification								
SARC-F	57.3 (45.9–68.2)	74.0 (69.3–78.4)	32.4 (27.1–38.2)	88.9 (86.0–91.2)	2.2 (1.7–2.8)	0.6 (0.4–0.7)	0.67 (0.63–0.71)	<0.001
SARC-CalF	86.6 (77.3–93.1)	66.8 (61.8–71.6)	36.2 (32.5–40.2)	95.8 (92.9–97.6)	2.6 (2.2–3.1)	0.2 (0.1–0.3)	0.83 (0.79–0.86)	
IWGS classification								
SARC-F	62.5 (48.5–75.1)	72.7 (68.1–77.0)	24.1 (19.7–29.2)	93.3 (90.8–95.2)	2.3 (1.8–3.0)	0.5 (0.4–0.7)	0.68 (0.64–0.72)	<0.001
SARC-CalF	91.1 (80.4–97.0)	57.3 (52.3–62.2)	22.9 (20.5–25.4)	97.9 (95.2–99.1)	2.1 (1.9–2.5)	0.2 (0.1–0.4)	0.80 (0.77–0.84)	
SCWD classification								
SARC-F	63.2 (46.0–78.2)	71.3 (66.7–75.5)	16.6 (13.0–20.9)	95.5 (93.4–97.0)	2.2 (1.7–2.9)	0.5 (0.3–0.8)	0.67 (0.62–0.71)	<0.001
SARC-CalF	86.8 (71.9–95.6)	61.3 (56.4–66.0)	16.8 (14.6–19.4)	98.1 (95.8–99.2)	2.2 (1.9–2.7)	0.2 (0.1–0.5)	0.80 (0.76–0.84)	
FNIH classification								
SARC-F	64.0 (42.5–82.0)	70.3 (65.7–74.5)	11.0 (8.2–14.7)	97.1 (95.2–98.3)	2.2 (1.6–3.0)	0.5 (0.3–0.9)	0.68 (0.64–0.72)	0.076
SARC-CalF	92.0 (74.0–99.0)	57.1 (52.3–61.9)	11.0 (9.5–12.7)	99.2 (97.0–99.8)	2.2 (1.8–2.5)	0.2 (0.1–0.5)	0.77 (0.73–0.81)	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; AUC, area under the ROC curves. Values within parentheses represent the 95% confidential intervals.

[a] *The p-value represents the difference between the SARC-F and SARC-CalF groups.*

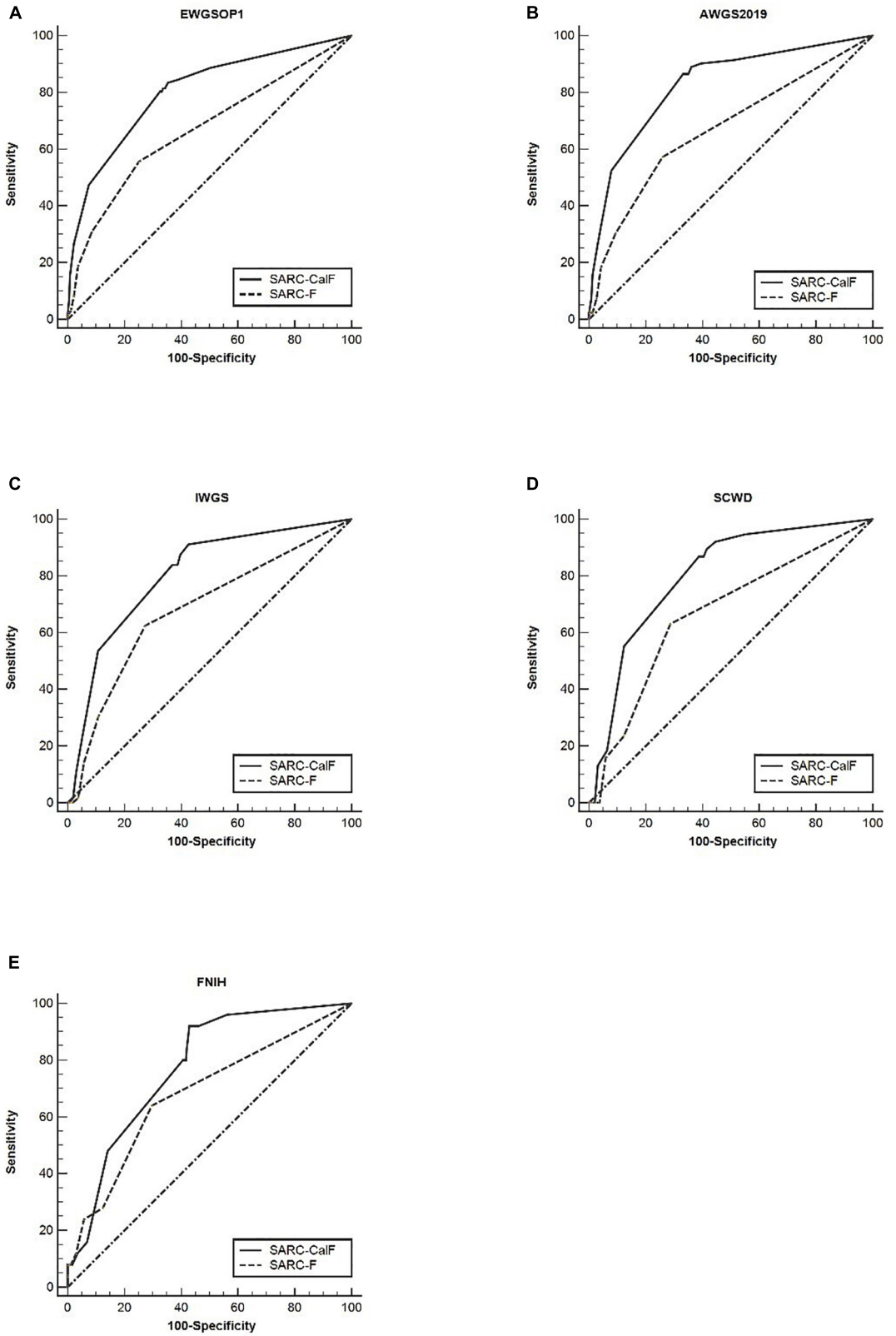

FIGURE 2 | The ROC curves of SARC-F and SARC-CalF compared with various reference standards in men: **(A)** sarcopenia according to the EWGSOP1 criteria; **(B)** sarcopenia according to AWGS2019 criteria; **(C)** sarcopenia according to IWGS criteria; **(D)** sarcopenia according to SCWD criteria; and **(E)** sarcopenia according to FNIH criteria.

Sarcopenia was defined according to the EWGSOP1 and AWGS2019 criteria as low muscle mass, in addition to low muscle strength or low physical performance. According to the IWGS and SCWD criteria, sarcopenia is defined as low muscle mass and poor physical performance. According to the FNHI recommendation, sarcopenia is defined as a low muscle mass associated with low muscle strength. Various diagnostic criteria recommended different cut-off values and were inconsistent for both sexes. The comprehensive criteria used in this study are listed in **Table 1**.

Statistical Analysis

SPSS software (version 23.0; SPSS Statistics, IBM, Armonk, NY, United States) and MedCalc statistical software (version 19.0; MedCalc software bvba, Ostend, Belgium) were used for statistical analysis. A two-tailed p-value of <0.05 was considered to indicate significant differences.

The clinical properties of the substances between men and women were compared. Continuous variables with a normal distribution were presented as mean ± SD. For continuous variables with skewed distributions, data were presented as the median (interquartile range). Student's t-test and Mann–Whitney U-test were used to compare continuous variables. For categorical variables, data were presented as numbers (percentage). The X^2 test was used to compare the categorical variables.

The EWGSOP1, AWGS2019, IWGS, SCWD, and FNIH were used as reference standards. The diagnostic value was calculated, for instance, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for SARC-F and SARC-CalF to screen for sarcopenia. The receiver-operating characteristic (ROC) curve was used to compare the overall diagnostic precision and calculate the area under the ROC curves (AUC) at a 95% confidence interval (CI). Overall, AUCs <0.5, 0.5–0.7, 0.7–0.9, and >0.9 demonstrate that a tool has no, low, moderate, and high diagnostic values (21). The AUC values for each ROC curve were compared using the DeLong method (22). The data were also stratified by age and sex to investigate the capacity and application of the two screening tools.

RESULTS

Subjects' Description and Characteristics

In total, 689 T2DM inpatients from our clinic were available for assessment. Regarding the population sample, there are about 459 men and 230 women with a mean age of 56.4 ± 13.6 years for men and 61.7 ± 11.7 years for women. The properties of the substances according to sex are summarized in **Table 2**. In accordance to the table, women had a higher mean age than men ($p < 0.001$), duration of diabetes ($p = 0.028$), 2hPG ($p = 0.023$), HOMA-IR ($p < 0.001$), SARC-F scores ($p < 0.001$), and SARC-ClaF scores ($p < 0.001$). In contrast, men had considerably higher levels of ALT ($p < 0.001$), AST ($p = 0.007$), CC ($p < 0.001$), HGS ($p < 0.001$), GS ($p < 0.001$), SMI ($p < 0.001$), and ASM/IMC ($p < 0.001$). Additionally, FPG, eGFR, BMI, and WC were not significantly different between the two groups.

Prevalence of Sarcopenia

Table 2 presents the incidence of sarcopenia according to the two screening instruments and the five diagnostic criteria. In the entire study population, the median scores for SARC-F and SARC-CalF were 0 and 3, respectively. Based on SARC-F and SARC-CalF, the prevalence of sarcopenia in our study population

TABLE 5 | Analysis of the curves of sensitivity, specificity, PPV, VPN, +LR, and −LR and ROC for the validation of SARC-F and SARC-CalF against various criteria of sarcopenia in women.

	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR	AUC	p-Value[a]
EWGSOP1 classification								
SARC-F	51.4 (34.0–68.6)	83.1 (77.1–88.1)	35.3 (25.9–46.0)	90.5 (87.1–93.1)	3.0 (1.9–4.8)	0.6 (0.4–0.8)	0.72 (0.65–0.77)	0.025
SARC-CalF	68.6 (50.7–83.1)	78.0 (71.5–83.6)	35.8 (28.3–44.1)	93.3 (89.4–95.8)	3.1 (2.2–4.4)	0.4 (0.2–0.7)	0.80 (0.74–0.85)	
AWGS2019 classification								
SARC-F	48.5 (30.8–66.5)	82.2 (76.2–87.3)	31.4 (22.4–42.1)	90.5 (87.2–93.0)	2.7 (1.7–4.3)	0.6 (0.4–0.9)	0.70 (0.63–0.75)	0.005
SARC-CalF	69.7 (51.3–84.4)	77.7 (71.2–83.3)	34.3 (27.0–42.4)	93.9 (90.1–96.3)	3.1 (2.2–4.4)	0.4 (0.2–0.7)	0.80 (0.74–0.85)	
IWGS classification								
SARC-F	38.5 (20.2–59.4)	79.9 (73.7–85.2)	19.6 (12.3–29.9)	91.1 (88.2–93.3)	1.9 (1.1–3.3)	0.8 (0.6–1.1)	0.61 (0.54–0.67)	0.006
SARC-CalF	88.5 (69.8–97.6)	48.0 (41.0–55.1)	17.8 (15.2–20.8)	97.0 (91.8–99.0)	1.7 (1.4–2.1)	0.2 (0.1–0.7)	0.73 (0.67–0.79)	
SCWD classification								
SARC-F	54.6 (23.4–83.3)	79.5 (73.5–84.6)	11.8 (6.8–19.5)	97.2 (94.8–98.5)	2.7 (1.5–4.8)	0.6 (0.3–1.1)	0.70 (0.64–0.76)	0.248
SARC-CalF	72.7 (39.0–94.0)	73.1 (66.7–78.8)	11.9 (8.2–17.1)	98.2 (95.3–99.3)	2.7 (1.8–4.1)	0.4 (0.1–1.0)	0.78 (0.72–0.83)	
FNIH classification								
SARC-F	50.0 (11.8–88.2)	78.6 (72.6–83.8)	5.9 (2.6–12.6)	98.3 (96.3–99.2)	2.3 (1.0–5.4)	0.6 (0.3–1.4)	0.62 (0.56–0.69)	0.227
SARC-CalF	66.7 (22.3–95.7)	71.9 (65.5–77.7)	6.0 (3.4–10.4)	98.8 (96.3–99.6)	2.4 (1.3–4.3)	0.5 (0.1–1.4)	0.70 (0.64–0.76)	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; AUC, area under the ROC curves. Values within parentheses represent the 95% confidential intervals.

[a] *The p-value represents the difference between the SARC-F and SARC-CalF groups.*

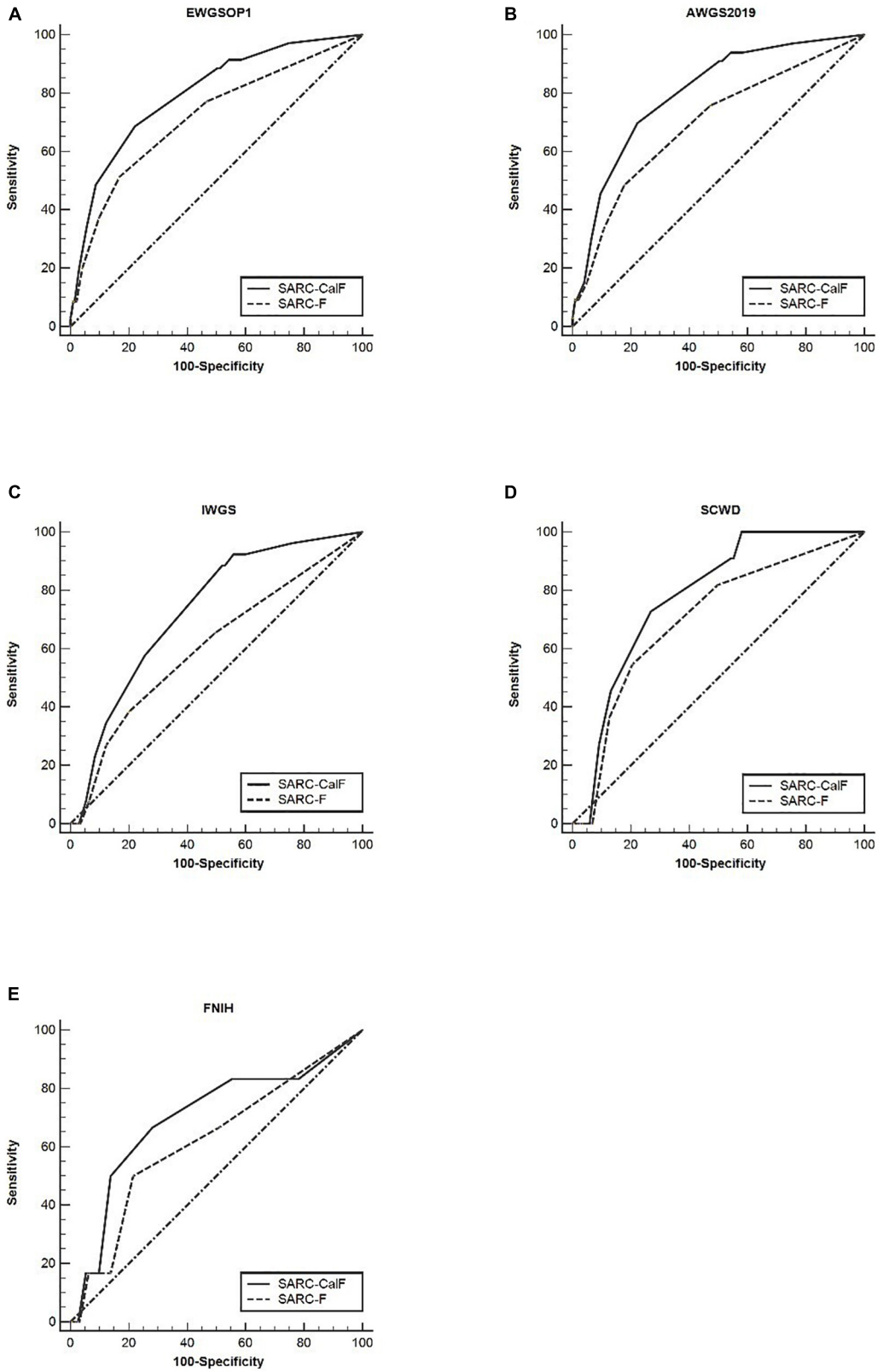

FIGURE 3 | The ROC curves of SARC-F and SARC-CalF compared with various reference standards in women: **(A)** sarcopenia according to the EWGSOP1 criteria; **(B)** sarcopenia according to AWGS2019 criteria; **(C)** sarcopenia according to IWGS criteria; **(D)** sarcopenia according to SCWD criteria; and **(E)** sarcopenia according to FNIH criteria.

was 4.5 and 20.3%, respectively. According to the recommended cut-off values for various diagnostic criteria, the prevalence of sarcopenia was 19.2, 16.7, 11.9, 7.1, and 4.5%. The prevalence of sarcopenia varied between 5.4 and 21.1% in men and 2.6 and 15.2% in women. Irrespective of the reference benchmarks applied, sarcopenia was more common in men than in women; however, the differences were not significant.

Comparison of SARC-F and SARC-CalF in the Whole Study Population

Table 3 presents the results of sensitivity/specificity analyses, as well as the AUC of SARC-F and SARC-CalF in the course of applying various diagnostic criteria as the reference benchmark. The sensitivity of the two tools varied in the following ranges: SARC-F, 61.4–67.4%; and SARC-ClaF, 82.6–91.8%. The values of the specificity ranges were as follows: SARC-F, 63.1–67.3%; and SARC-ClaF, 51.5–61.2%. The PPV outcomes ranged from 7.6% (for SARC-F against FNIH) to 33.5% (for SARC-CalF against EWGSOP1), while a deviation is recorded in NPV as it varies from 88.0% (for SARC-F against EWGSOP1) to 99.1% (for SARC-CalF against FNIH). Irrespective of the type of diagnostic criteria utilized as the reference standard, compared to the SARC-F, the SARC-CalF had more suitable sensitivity and lower specificity.

As shown in **Figure 1**, the ROC curves of the two screening tools against various standards in the entire study population are plotted. The ranges of AUCs of SARC-F and SARC-CalF are 0.65–0.67 and 0.74–0.81, respectively. Regarding the AUCs, unless the FNIH criteria were implemented, the variation between SARC-F and SARC-CalF was statistically significant ($p < 0.001$). When comparing the two screening tools, the SARC-CalF had the most significant AUC but only against the AWGS2019 criteria (0.81). These outcomes indicate that a nearly high level of diagnostic value was recorded. In contrast, the least AUC against the IWGS and FNIH criteria was recorded in SARC-F (0.65), and it likewise had a correspondingly small AUC for EWGSOP (0.67), AWGS2019 (0.67), and SCWD (0.66).

Comparison of SARC-F and SARC-CalF in Each Sex

Table 4 presents the results of sensitivity/specificity analyses and AUCs of SARC-F and SARC-CalF in humans using various diagnostic criteria as reference standards. In men, SARC-CalF displayed more suitable sensitivity as a reference standard, regardless of diagnostic criteria; however, in contrast with SARC-F, it displays a lower specificity. For instance, using EWGSOP1 as a reference standard, the sensitivities of SARC-F and SARC-CalF were 55.7 and 83.5%, and the specificities were 74.9 and 64.6%, respectively. In **Figure 2**, the ROC curves for SARC-F and SARC-CalF against various reference standards in men are depicted. Through the application of the EWGSOP1 criteria, the respective AUC values for SARC-F and SARC-CalF were 0.67 and 0.80. Therefore, the difference was significant ($p < 0.001$). In this study, the corresponding outcomes were obtained using AWGS2019, IWGS, and SCWD. Assuming that the FNIH criteria were applied, there was no significant difference ($p = 0.076$).

Table 5 presents the results of sensitivity/specificity analyses, as well as the AUCs of SARC-F and SARC-CalF in women with diverse diagnostic criteria serving as a reference benchmark. Regardless of the adopted reference standard utilized for women, SARC-CalF equally demonstrated more suitable sensitivity and identical specificity in contrast to SARC-F. For instance, when using EWGSOP1 as the reference standard, the sensitivities of SARC-F and SARC-CalF were 51.4 and 68.6%, and the specificities were 83.1 and 78.0%, respectively. The ROC curves for SARC-F and SARC-CalF against various reference standards

TABLE 6 | Sensitivity, specificity, PPV, VPN, +LR, and −LR tests and ROC curves for SARC-F and SARC-CalF validation against various sarcopenia criteria in the older group.

	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR	AUC	*p*-Value[a]
EWGSOP1 classification								
SARC-F	41.1 (30.8–52.0)	80.7 (75.0–85.6)	45.1 (36.4–54.1)	78.0 (74.7–81.0)	2.1 (1.5–3.1)	0.7 (0.6–0.9)	0.63 (0.57–0.68)	<0.001
SARC-CalF	84.4 (75.3–91.2)	54.9 (48.3–61.4)	42.0 (38.0–46.1)	90.1 (84.8–93.8)	1.9 (1.6–2.2)	0.3 (0.2–0.5)	0.75 (0.70–0.80)	
AWGS2019 classification								
SARC-F	42.5 (31.0–54.6)	79.6 (74.1–84.4)	37.8 (29.7–46.6)	82.6 (79.4–85.4)	2.1 (1.4–3.0)	0.7 (0.6–0.9)	0.64 (0.58–0.69)	<0.001
SARC-CalF	90.4 (81.2–96.1)	54.0 (47.6–60.3)	36.5 (33.0–40.1)	95.1 (90.4–97.5)	2.0 (1.7–2.3)	0.2 (0.1–0.4)	0.78 (0.74–0.83)	
IWGS classification								
SARC-F	66.0 (51.7–78.5)	51.9 (45.7–57.9)	21.2 (17.6–25.3)	88.6 (84.0–92.0)	1.4 (1.1–1.7)	0.7 (0.4–1.0)	0.60 (0.54–0.65)	<0.001
SARC-CalF	88.7 (77.0–95.7)	50.4 (44.2–56.5)	26.0 (23.1–29.0)	95.8 (91.4–98.0)	1.8 (1.5–2.1)	0.2 (0.1–0.5)	0.73 (0.68–0.78)	
SCWD classification								
SARC-F	69.0 (49.2–84.7)	50.7 (44.8–56.5)	12.1 (9.5–15.3)	94.3 (90.5–96.6)	1.4 (1.1–1.8)	0.6 (0.4–1.1)	0.59 (0.53–0.64)	<0.001
SARC-CalF	93.1 (77.2–99.2)	47.6 (41.8–53.5)	14.9 (13.1–16.9)	98.6 (94.8–99.6)	1.8 (1.5–2.1)	0.2 (0.1–0.6)	0.73 (0.68–0.78)	
FNIH classification								
SARC-F	68.0 (46.5–85.1)	50.3 (44.5–56.2)	10.3 (7.9–13.3)	94.9 (91.3–97.1)	1.4 (1.0–1.8)	0.6 (0.4–1.1)	0.60 (0.54–0.65)	0.195
SARC-CalF	92.0 (74.0–99.0)	42.0 (36.3–47.8)	11.7 (10.3–13.4)	98.4 (94.3–99.6)	1.6 (1.4–1.8)	0.2 (0.1–0.7)	0.67 (0.61–0.72)	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; AUC, area under the ROC curves. Values within parentheses represent the 95% confidential intervals. [a]The p-value represents the difference between the SARC-F and SARC-CalF groups.

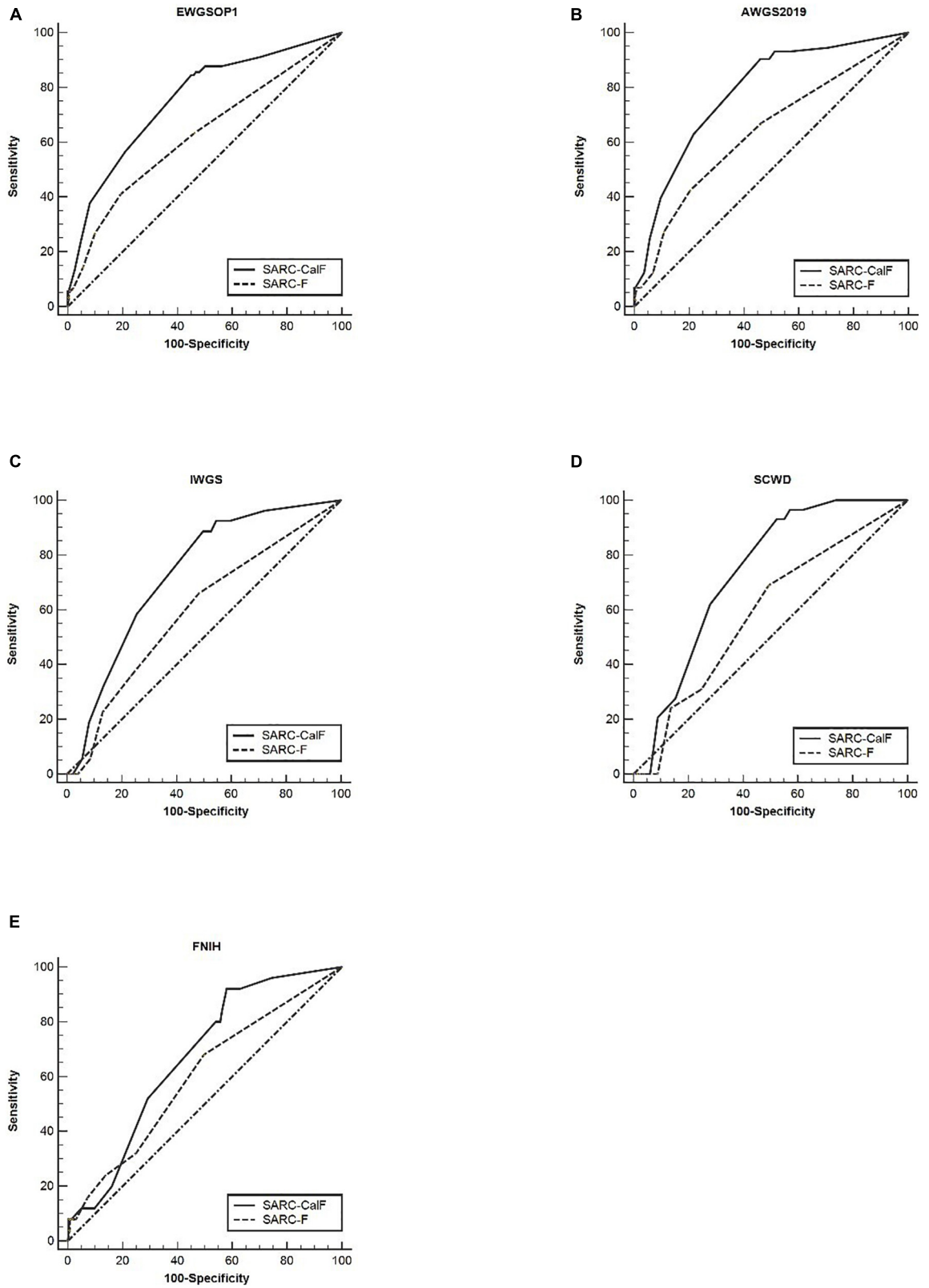

FIGURE 4 | The ROC curves of SARC-F and SARC-CalF compared with various reference norms in the older group: **(A)** sarcopenia according to the EWGSOP1 criteria; **(B)** sarcopenia according to AWGS2019 criteria; **(C)** sarcopenia according to IWGS criteria; **(D)** sarcopenia according to SCWD criteria; and **(E)** sarcopenia according to FNIH criteria.

in women are shown in **Figure 3**. Using the EWGSOP1 criteria, the AUCs for SARC-F and SARC-CalF were 0.72 and 0.80, respectively. There was a significant difference between the groups (p = 0.025). With the assistance of AWGS2019 and IWGS, similar results were obtained. The AUC of SARC-CalF is moderate when applied to different sensitivities to various reference benchmarks when applied for different sexes.

Comparison of SARC-F and SARC-CalF in Each Age Group

Table 6 presents the screening potential of SARC-F alongside SARC-CalF in subjects aged ≥60 years during the application of various diagnostic criteria as reference standards. Sensitivity/specificity analyses showed related results in the older group, in contrast to the entire study population. The sensitivity of the two instruments varied in the following areas: SARC-F, 41.1–69.0%; and SARC-CalF, 84.4–93.1%. The ranges of specificity were as follows: SARC-F, 50.3–80.7%; and SARC-CalF, 42.0–54.9%. As shown in **Figure 4**, during the process of applying the EWGSOP1, AWGS2019, IWGS, and SCWD, the variation in AUC between SARC-F and SARC-CalF was generally significant. **Table 7** presents the screening potentials of SARC-F and SARC-CalF in subjects aged <60 years with varying diagnostic criteria as a reference standard. In the younger group, the sensitivity of the two instruments varied in the following areas: SARC-F, 33.3–65.0%; and SARC-Calf, 83.3–90.0%. The ranges of specificity were as follows: SARC-F, 75.4–92.2%; and SARC-CalF, 59.3–62.4%. As shown in **Figure 5**, there is a significant variation in AUC between SARC-F and SARC-CalF when the EWGSOP1, AWGS2019, and IWGS criteria were applied.

In the category of older subjects, the AUC of the two instruments was from 0.59 to 0.78, while it was from 0.64 to 0.82 in younger subjects. Therefore, a comparison of both groups demonstrated that the AUC of the two screening tools was higher in the younger subjects than in the older subjects. Furthermore, it was observed that the increase in age is directly proportional to the increase in sensitivity to SARC-CalF. In contrast, a contradictory trend was demonstrated in the specificity of SARC-CalF.

DISCUSSION

This study showed that SARC-CalF was significantly more suitable than SARC-F in sarcopenia screening for patients with T2DM in terms of sensitivity and general diagnostic accuracy using varying criteria as a gold benchmark. Since sarcopenia is associated with serious consequences on the health of older subjects, early recommendation of preventive strategies is highly necessary. Thus, from a clinical perspective, it is essential to provide an early diagnosis using simple and effective sarcopenia screening tools, preferably, a screening tool exhibiting high sensitivity while simultaneously maintaining high specificity (23).

Based on the general consensus about sarcopenia, for diagnosis confirmation, it has been demonstrated that low muscle mass and function are essential. SARC-F is the first screening tool for sarcopenia and has been widely applied in the field of sarcopenia. Thus far, the validation of the research has been implemented in China (8, 12, 24), America (25), Japan (26), Turkey (10), and Brazil (27, 28), to mention a few. Nevertheless, previous studies have revealed that it has high specificity and low sensitivity. A novel study conducted by Parra-Rodríguez et al. revealed that in 487 men and women, the sensitivity to SARC-F was 35.6% with a specificity of 82.2% (9). The outcome of this study corresponds to the results of Woo et al., which revealed that the sensitivity and specificity of SARC-F were 9.9 and 94.4%,

TABLE 7 | Sensitivity, specificity, PPV, NPV, +LR, and −LR assessments and ROC curves for SARC-F and SARC-CalF validation against various criteria of sarcopenia in the group comprising of the younger group.

	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR	AUC	*p*-Value[a]
EWGSOP1 classification								
SARC-F	57.1 (41.0–72.3)	77.2 (72.2–81.6)	24.5 (18.9–31.1)	93.3 (90.7–95.2)	2.5 (1.8–3.5)	0.6 (0.4–0.8)	0.69 (0.64–0.73)	0.005
SARC-CalF	83.3 (68.6–93.0)	61.7 (56.2–67.0)	22.0 (18.9–25.5)	96.6 (93.5–98.3)	2.2 (1.8–2.6)	0.3 (0.1–0.5)	0.80 (0.76–0.84)	
AWGS2019 classification								
SARC-F	54.8 (38.7–70.2)	76.9 (71.9–81.3)	23.5 (17.9–30.1)	92.9 (90.3–94.8)	2.4 (1.7–3.3)	0.6 (0.4–0.8)	0.67 (0.62–0.72)	<0.001
SARC-CalF	88.1 (74.4–96.0)	62.4 (56.8–67.6)	23.3 (20.2–26.6)	97.6 (94.6–98.9)	2.3 (2.0–2.8)	0.2 (0.1–0.4)	0.82 (0.77–0.85)	
IWGS classification								
SARC-F	58.6 (38.9–76.5)	76.0 (71.0–80.4)	17.3 (12.8–23.1)	95.5 (93.2–97.1)	2.4 (1.7–3.5)	0.5 (0.4–0.8)	0.68 (0.63–0.73)	0.017
SARC-CalF	89.7 (72.6–97.8)	60.5 (55.1–65.8)	16.4 (14.0–19.0)	98.6 (95.9–99.5)	2.3 (1.9–2.7)	0.2 (0.1–0.5)	0.79 (0.75–0.83)	
SCWD classification								
SARC-F	65.0 (40.8–84.6)	75.4 (70.5–79.9)	13.3 (9.5–18.1)	97.4 (95.3–98.5)	2.7 (1.8–3.8)	0.5 (0.3–0.8)	0.72 (0.67–0.76)	0.090
SARC-CalF	90.0 (68.3–98.8)	59.3 (53.9–64.5)	11.3 (9.5–13.4)	99.0 (96.5–99.7)	2.2 (1.8–2.7)	0.2 (0.1–0.6)	0.80 (0.76–0.84)	
FNIH classification								
SARC-F	33.3 (4.3–77.7)	92.2 (89.0–94.8)	6.7 (2.1–19.0)	98.8 (97.9–99.3)	4.3 (1.3–14.0)	0.7 (0.4–1.3)	0.64 (0.59–0.69)	0.143
SARC-CalF	83.3 (35.9–99.6)	61.4 (56.1–66.4)	3.5 (2.4–5.0)	99.5 (97.4–99.9)	2.2 (1.5–3.2)	0.3 (0.1–1.6)	0.77 (0.72–0.81)	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; AUC, area under the ROC curves. Values within parentheses represent the 95% confidential intervals.

[a] *The p-value represents the difference between the SARC-F and SARC-CalF groups.*

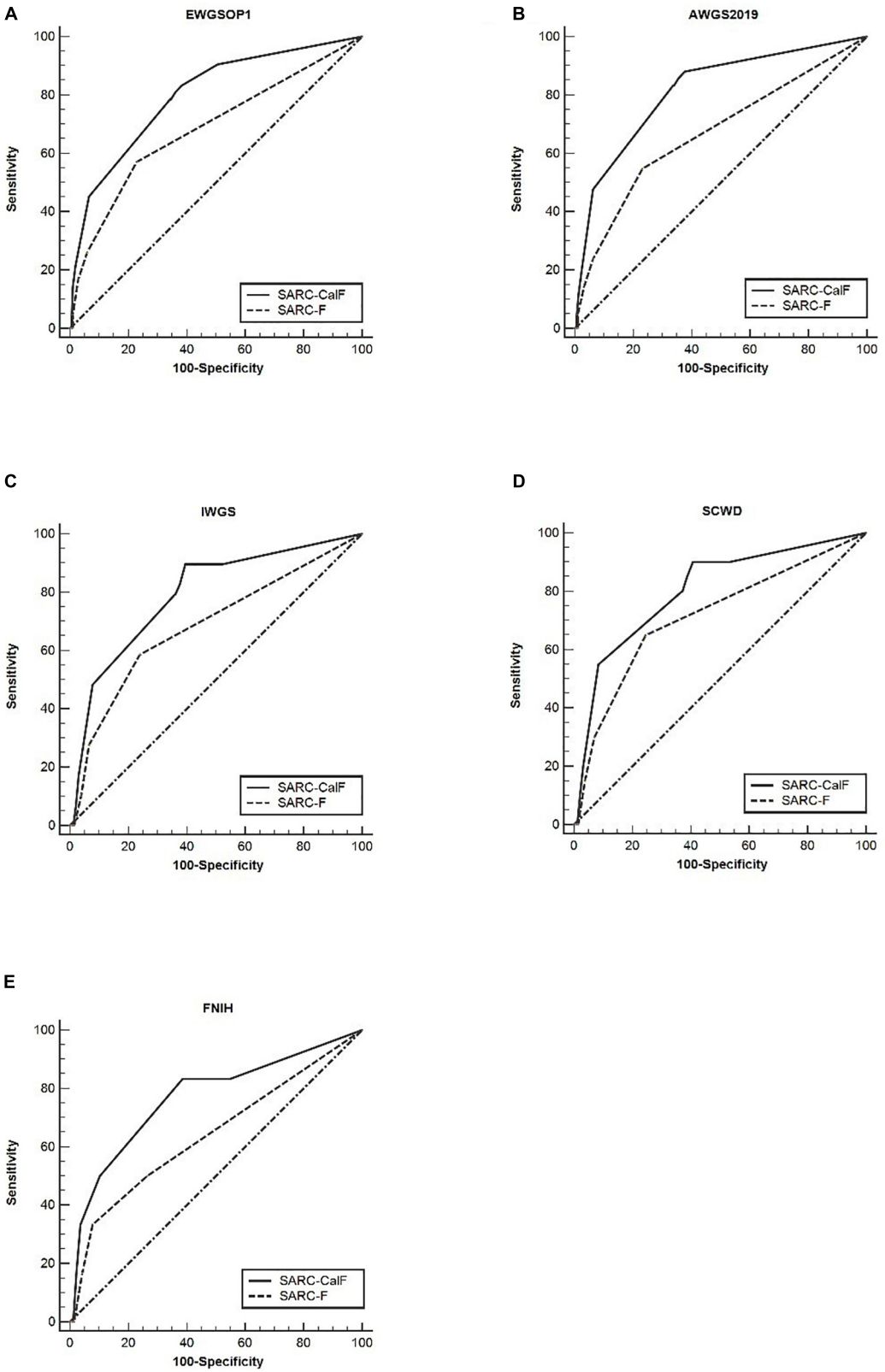

FIGURE 5 | The ROC curves of SARC-F and SARC-CalF compared with various reference standards in the category of younger subjects: **(A)** sarcopenia according to the EWGSOP1 criteria; **(B)** sarcopenia according to AWGS2019 criteria; **(C)** sarcopenia according to IWGS criteria; **(D)** sarcopenia according to SCWD criteria; and **(E)** sarcopenia according to FNIH criteria.

respectively (8). Thus, due to the low sensitivity of SARC-F, it has subsequently brought about limitations to its clinical application.

From the findings of Kawakami et al., a positive correlation was found between CC and muscle mass (29). Furthermore, the SARC-CalF, integrating CC and SARC-F, was developed by Barbosa-Silva. This research, which involved 179 older people in communities in Brazil, found that the sensitivity and specificity of SARC-CalF were 66.7 and 82.9%, respectively (11). Following the application of the same standard, it was reported by Yang et al. that SARC-CalF with sensitivity and specificity in Chinese nursing home occupants was 58.9 and 84.5%, respectively (13). Therefore, it was proposed by the above researchers that SARC-CalF should be utilized as a modified version for enhancing the sensitivity of SARC-F (11). In this study, the sensitivity and specificity displayed by SARC-CalF were 82.6 and 61.2%, respectively, by applying the EWGSOP1 criteria. In contrast to past research, this study showed relatively lower specificity, albeit a higher sensitivity, possibly as a result of the varying clinical features (race, sex, and age) of the subjects. In addition, all subjects in the study have diabetes. Applying various diagnostic criteria, the AUC of SARC-F ranged from 0.65 to 0.67, and the AUC of SARC-CalF ranged from 0.74 to 0.81. Thus, SARC-F displayed low diagnostic precision, and SARC-CalF demonstrated moderate diagnostic accuracy. In general, with regard to the screening for sarcopenia in adults with T2DM, SARC-CalF is more effective than SARC-F.

This study demonstrated that sex and age could affect the screening potential of the two screening tools. Overall, men tend to overestimate their physical abilities (30), while women could underestimate their physical abilities because of their diverse perceptions. The results of this study showed that SARC-F and SARC-CalF have significantly higher values in women than in men. Regarding sex, SARC-CalF in men showed higher sensitivity and AUC compared with women. This result in contrast to the conclusion of Mo et al. (31). Moreover, age was one of the criteria. In general, the specificity and AUC of SARC-CalF decreased with age. In contrast, the trend displayed by the sensitivity of SARC-CalF showed the opposite trend. This result corroborate the study by Mo et al. (31).

Calf circumference tends to be profoundly impacted by obesity and edema, which may mask sarcopenia (13, 32). Nevertheless, various optimal cut-off points exist for CC in various ethnic groups. Kawakami et al. utilized 34 and 33 cm as cut-off points for CC in Japanese men and women, respectively, in estimating low muscle mass (29). In a Turkish study, 33 cm was proposed as the threshold point for CC in men and women (33). In a recent study conducted by Hwang et al. in Taiwan, sections were recorded at 33 and 32 cm to predict sarcopenia in men and women, respectively. In our study, the median CC in men and women was 34 and 33 cm, respectively. Thus, the cut-off values of the screening recommended by the AWGS2019 consensus are appropriate for subjects utilized in this study.

Recent studies have reported that the CC *per se* was better than the SARC-F and SARC-CalF (31, 34, 35). Our data demonstrated that although both the SARC-CalF and CC outperformed the SARC-F, demonstrating moderate diagnostic accuracy; the CC *per se* was not significantly better than the SARC-CalF. In contrast, the SARC-CalF was slightly more sensitive than the CC. This finding should be addressed in future studies with larger sample sizes. Overall, the conclusions remain unchanged. These data are shown in **Supplementary Table 2**. Moreover, a novel tool, known as the mini sarcopenia risk assessment (MSRA) questionnaire, was developed by Rossi et al., with sensitivity and specificity of 80.4 and 60.4%, respectively. The MSRA includes a comprehensive evaluation and nutritional assessment (36). This scale was validated in the study by Ming-Yang et al. in various populations and subsequently surmised that MSRA-5 could act as a dependable and valid tool for screening sarcopenia (13, 37). Through the application of age, as well as BMI, Kurita et al. enhanced SARC-F and named this modified version SARC-F + EBM (38). In 2019, research conducted on 959 hospitalized Japanese patients showed that SARC-F + EBM had higher sensitivity than SARC-F, with a sensitivity of 77.8% and a specificity of 69.6% (38). Thus, the validation and comparison of these new screening tools in adults with T2DM should be evaluated in subsequent studies.

Certain drawbacks of this study need to be addressed. First, this study focused initially only on hospitalized patients with T2DM. Thus, this study outcome may not be appropriate for older people residing in the community. Second, cognitive functions were not assessed because our subjects were relatively young. Notwithstanding, SARC-F was developed based on the elderly population. Third, the prognostic value of SARC-F and SARC-CalF for adverse outcomes should be considered in future prospective studies as a cross-sectional study.

CONCLUSION

In summary, early detection and intervention of sarcopenia are crucial. Regardless of the reference standard, sex, and age, SARC-CalF displayed more suitable sensitivity and diagnostic performance than SARC-F. Thus, SARC-CalF appears to be a more appropriate screening tool for sarcopenia in adults with T2DM. Subsequent research is needed to validate the utility of SARC-CalF in various populations and frameworks.

STANDARD BIOSECURITY AND INSTITUTIONAL SAFETY PROCEDURES

All institutional security procedures were followed and biosecurity metrics were implemented. The hospital laboratory utilized for this research has a biosafety level 2 (BSL-2) standard, implying that all standards and protocols have been implemented in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

HZ conceived and designed this manuscript. JJ, ZZ, and YC conducted the data collection and participants' recruiting exercises. HZ and ZX conducted the data analysis and interpretation. ZX and PZ prepared the manuscript. All authors in this study contributed to the article and subsequently 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.2022.803924/full#supplementary-material

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Correlation Among Body Composition Parameters and Long-Term Outcomes in Crohn's Disease After Anti-TNF Therapy

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Background: The impact of the body composition on the pathophysiology and clinical course of Crohn's disease (CD) has not been fully elucidated.

Aims: To reveal the correlations among body composition and long-term outcomes in CD after anti-TNF therapy.

Methods: *Ninety-one* patients who received anti-TNF therapy as their first biologic treatment were enrolled. The skeletal muscle index (SMI), visceral and subcutaneous fat area (VFA, SFA), and the ratio of the VFA to SFA (mesenteric fat index; MFI) at the 3rd lumbar level were measured using computed tomography (CT) imaging before the induction. The correlation among the body composition and outcomes were retrospectively analyzed.

Results: The 5-year cumulative secondary failure- and resection-free rates in patients with a low SMI (39.1% and 64.8%) were significantly lower than those with a high SMI (67.5% and 92.7%; $p = 0.0071$ and 0.0022, respectively). The 5-year cumulative secondary failure-free rate in the patients with low VF (45.0%) was significantly lower than that in those with high VF (77.6%; $p = 0.016$), and the 5-year cumulative resection-free rate in patients with a high MFI (68.9%) was significantly lower than that in those with a low MFI (83.0%; $p = 0.031$). Additionally, patients with low age and BMI had significantly lower cumulative secondary failure- and resection-free rates than those with high age and BMI (low age: 37.4% and 71.2%; high age: 70.7% and 88.9%; $p = 0.0083$ and 0.027, respectively) (low BMI: 27.2% and 64.8%; high BMI: 68.3% and 87.9%; $p = 0.014$ and 0.030, respectively), respectively. In the multivariate analyses, a low SMI was the only independent risk factor for secondary failure (hazard ratio [HR] 2.15, 95% confidence interval [CI] 1.04–4.44), while low age (HR 4.06, 95% CI 1.07–15.4), a low SMI (HR 4.19, 95% CI 1.01–17.3) and high MFI were risk factors for bowel resection (HR 4.31, 95% CI 1.36–13.7).

Conclusion: The skeletal muscle mass and ratio of visceral to subcutaneous fat were suggested to reflect the long-term clinical outcome and may be helpful as prognostic markers after anti-TNF therapy in CD.

Keywords: Crohn's disease, body composition, skeletal muscle, visceral fat, mesenteric fat index, anti-TNF antibody

INTRODUCTION

Crohn's disease (CD) is a relapsing and progressive chronic inflammatory intestinal disorder that leads to intestinal stenosis, abdominal abscess, fistula and bowel resection (1). Several studies have reported that more than half of CD patients are complicated with malnutrition, even in a remission state (2, 3). Malnutrition in CD is caused by multiple factors, including decreased oral food intake, medications such as corticosteroids, malabsorption, and increased energy expenditure (4). Malnutrition with CD is strongly associated with micronutrient and vitamin deficiency and alterations of the body composition including subcutaneous and visceral fat (SF and VF) and skeletal muscle mass (4). However, previous studies have reported that the body mass index (BMI) does not always reflect the body composition, as defined by fat and skeletal muscle mass, in CD patients (3, 5–7). In addition, alterations of subcutaneous and visceral fat and skeletal muscle mass in CD have been suggested to be regarded as biomarkers that reflect the disease phenotype (8, 9), activity (9), treatment response (7) and outcome, including bowel resection (10–12) and complications after surgery (13, 14). Therefore, the measurement of fat and skeletal muscle mass in CD were suggested to be crucial for predicting the disease course, as well as BMI and disease activity. Recently, the measurement and analysis of fat and skeletal muscle using abdominal computed tomography (CT) at the third lumbar level have been reported to be reliable and to have potential application as predictive biomarkers for not only inflammatory bowel disease, including CD (15–17), but also cancer, obesity and liver disease (18–21). Abdominal computed tomography (CT) is routinely utilized to assess the extent and complications of disease in clinical practice for CD. Therefore, abdominal CT is a more convenient and accessible tool for the analysis of the body composition in routine care for CD patients in comparison to whole body dual-energy X-ray absorptiometry (DXA).

According to a meta-analysis, the risk of surgery in CD at 5 and 10 years after the diagnosis of CD has been reported to be as high as 33.3 and 46.6%, respectively (22); however, the rate of surgery in CD has decreased over time (22, 23). Previous studies have suggested that the earlier induction of anti-TNF therapy remarkably contributed to a reduction in the surgery rate in CD (24–26). However, the annual rate of secondary loss of response (LOR) to anti-TNF therapy per patient-year in CD is reported to be 13–20% (27). Various factors have been reported to predict a non-response to anti-TNF therapy, including disease-related marker including fecal calprotectin, smoking, serological and genetic markers (28), while the association with the body composition has not been fully elucidated. The BMI at the induction has been revealed as a predictor of the drug concentration after 6 months and dose escalation (29, 30). A previous report revealed that a low muscle mass at the initiation of anti-TNF therapy for IBD was a risk factor for a LOR to anti-TNF therapy in the short term (31). However, no studies analyzing the correlation among body composition and long-term outcomes, including the need for surgery, as well as the rate of secondary failure in anti-TNF naïve CD patients have been demonstrated. This study aimed to reveal the correlation among body composition and long-term outcomes in patients with CD after anti-TNF therapy.

METHODS

Study Population

A total of 200 consecutive anti-TNF naïve CD patients in whom anti-TNF-α antibody therapy had been initiated were identified from a chart review at Asahikawa Medical University Hospital (Japan) between January 2007 and December 2018. Among them, 91 patients with anti-TNF-naïve CD in whom anti-TNF-α antibody therapy was initiated, and who met the following criteria, were enrolled in this study: (1) anti-TNF antibody was induced for the treatment of intestinal symptoms and/or lesions, (2) observational period after TNF therapy $\geq$1 year, (3) computed tomography was performed within 1 month before the administration of anti-TNF-α antibody therapy. Patients with only perianal disease or extraintestinal manifestations were excluded. This study retrospectively analyzed the correlation among the body composition parameters and long-term clinical outcomes after the induction of anti-TNF therapy in CD.

This study protocol was approved by the Ethics Committee of Asahikawa Medical University (Registry Number: 18235). Informed consent was obtained by announcing this study on the web and providing an opportunity to opt out.

Data Collection

The following patient characteristics before the administration of anti-TNF-α antibody therapy were collected from the patients' medical records: age, sex, height, body weight (BW), body mass index (BMI), type of disease extension (ileitis, ileo-colitis, colitis type), disease duration (from the development of CD), disease duration until the induction of anti-TNF-α antibody therapy, type of anti-TNF-α antibody (infliximab or adalimumab), presence or absence of concomitant immunomodulator usage. The following laboratory data before the administration of anti- TNF-α antibody therapy were also collected from medical records: white blood cell, neutrophil and lymphocyte counts, and the serum levels of C-reactive protein, albumin, total

cholesterol. The periods until the occurrence of secondary failure and/or bowel resection were collected from medical records, which were regarded as indicators of the long-term clinical outcome after the administration of anti-TNF-α antibody therapy. If a loss of response was suspected in clinical practice, endoscopy (ileocolonoscopy with or without balloon or capsule enteroscopy) and/or imaging studies (ultrasonography, CT and magnetic resonance imaging) in combination with a stool culture test (including clostridium) was performed to confirm the presence of worsening of endoscopic and/or imaging (transmural and extraintestinal) findings and to rule out the enteral infection. Secondary failure was defined by the following criteria (1 + [2 and/or 3]: (1) loss of response (worsening of clinical symptoms in combination with endoscopic and/or imaging findings) after a primary response to anti-TNF-α antibody therapy (after the induction phase), (2) strengthening and/or alteration of anti-TNF therapy, which included increasing the dose and shortening the duration of anti-TNF-α antibody therapy, alteration of biologics and the addition of concomitant therapy (immunomodulator, steroids and cytapheresis), and (3) the aggravation of gastrointestinal lesions on endoscopy and/or surgical specimens. In addition, bowel resection was defined as resection of the small and/or large intestine due to worsening intestinal symptoms and/or lesions after the induction of anti-TNF-α antibody therapy with or without stoma construction.

Measurements of the Skeletal Muscle and Fat Area

The skeletal muscle area (SMA) [cm^2], psoas muscle area (PMA) and visceral and subcutaneous fat area (VF [cm^2], SF [cm^2]) in addition to abdominal circumference (AC [cm]) at the 3rd lumbar level were measured from CT imaging before the induction of anti-TNF therapy, using the SYNAPSE VINCENT software program (Fuji Film, Tokyo, Japan). The skeletal muscle mass index (SMI [cm^2/m^2]) and psoas muscle index (PMI [cm^2/m^2]) was calculated as the respective muscle area divided by the square of height. The mesenteric fat mass index (MFI) was calculated as the ratio of VF to SF. SMA/SF was calculated as the ratio of SMA to SF.

Statistical Analyses

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Australia). The difference in measurements between male and female patients was compared with an unpaired *t*-test. The cut-off values of measurements for classification into two groups were determined with a receiver operating characteristics (ROC) analysis, the outcome of which was established as the presence or absence of secondary failure. Cut-off values were determined based on the threshold nearest to the top-left corner of the ROC curve. The cumulative secondary failure-free and bowel resection-free rates were calculated with the Kaplan-Meier method. The cumulative secondary failure-free and bowel resection-free rates were classified into two groups based on cut-off values and the groups were compared with a log-rank test. Bonferroni correction was applied in cases involving the comparison among more than three groups. The risk factors for secondary failure and bowel resection were analyzed with a Cox proportional hazards model, which included parameters that were identified as significant in a log-rank test. $P < 0.05$ were considered to indicate statistical significance.

TABLE 1 | Patient demographics.

Age at the induction of anti-TNF-α antibody therapy (years) (mean ± SD)	32.7 ± 14.9
Sex (M/F)	69/22
Height (cm) (mean ± SD)	166.2 ± 8.5
Body weight (kg) (mean ± SD)	55.8 ± 11.8
BMI (kg/m^2) (mean ± SD)	20.1 ± 3.3
AC (cm) (mean ± SD)	74.3 ± 9.3
Disease background at the induction of anti-TNF-α antibody therapy	
Type of disease (I/IC/C)	20/54/17
Disease duration (Months) (mean ± SD)	144.4± 106.4
Disease duration until the induction of anti-TNF-α antibody therapy (Months) (mean ± SD)	60.4 ± 78.3
Type of anti-TNF-α antibody	
Infliximab/Adalimumab, N (%)	74 (81.3%) /17 (18.7%)
Concomitant immunomodulator usage, N (%)	21 (23.1 %)
Average observation period (months)	61.9 ± 41.5
Laboratory data before the induction of anti-TNF-α antibody therapy	
WBC (/μl) (mean ± SD)	5,846 ± 2,475
TLC (/μl) (mean ± SD)	1,090 ± 490
Serum Alb (g/dl) (mean ± SD)	3.5 ± 0.59
T-Chol (mg/dl) (mean ± SD)	131.3 ± 28.1
CRP (mg/dl) (mean ± SD)	2.0 ± 3.3

BMI, Body mass index; AC, Abdominal circumference; I/IC/C, Ileitis/Ileo-colitis/Colitis; WBC, White blood cell count; TLC, Total lymphocyte count; Alb, Albumin; T-Chol, Total cholesterol; CRP, C-reactive protein.

RESULTS

Characteristics and Measurements of the Patients

The characteristics and laboratory data of 91 patients with CD before the induction of anti-TNF-α antibody therapy are summarized in **Table 1**. The body composition measurements are described in **Supplementary Table 1**. The average of VFA was 41.6 ± 38.1 (mean ±SD) (Male; 44.6 ± 38.2, Female; 32.1± 37.4, $p = 0.183$), the average SFA was 65.0 ± 55.8 (M; 59.8 ± 54.9, F; 81.0± 56.4, $p = 0.122$), and the average MFI was 0.82 ± 0.59 (M; 0.91 ± 0.54, F; 0.53± 0.64, $p = 0.0078$). The average SMA was 111.3 ± 30.5 (M; 122.1 ± 25.8, F; 77.6± 16.1, $p < 0.0001$), the average SMI was 39.8 ± 9.1 (M; 42.6 ± 8.3, F; 31.1 ± 5.2, $p < 0.0001$), PMA was 15.7 ± 5.6 (M; 17.8 ± 4.4, F; 9.0± 2.8, $p < 0.0001$), and the average PMI was 5.5 ± 1.8 (M; 6.1 ± 1.6, F; 3.6 ± 1.0, $p < 0.0001$). The average SMA/SF was 3.5 ± 3.7 (M; 4.1 ± 4.0, F; 1.5 ± 1.0, $p = 0.0029$). All measurements associated with skeletal muscle area showed significant differences between males and females while the actual measurement value of the

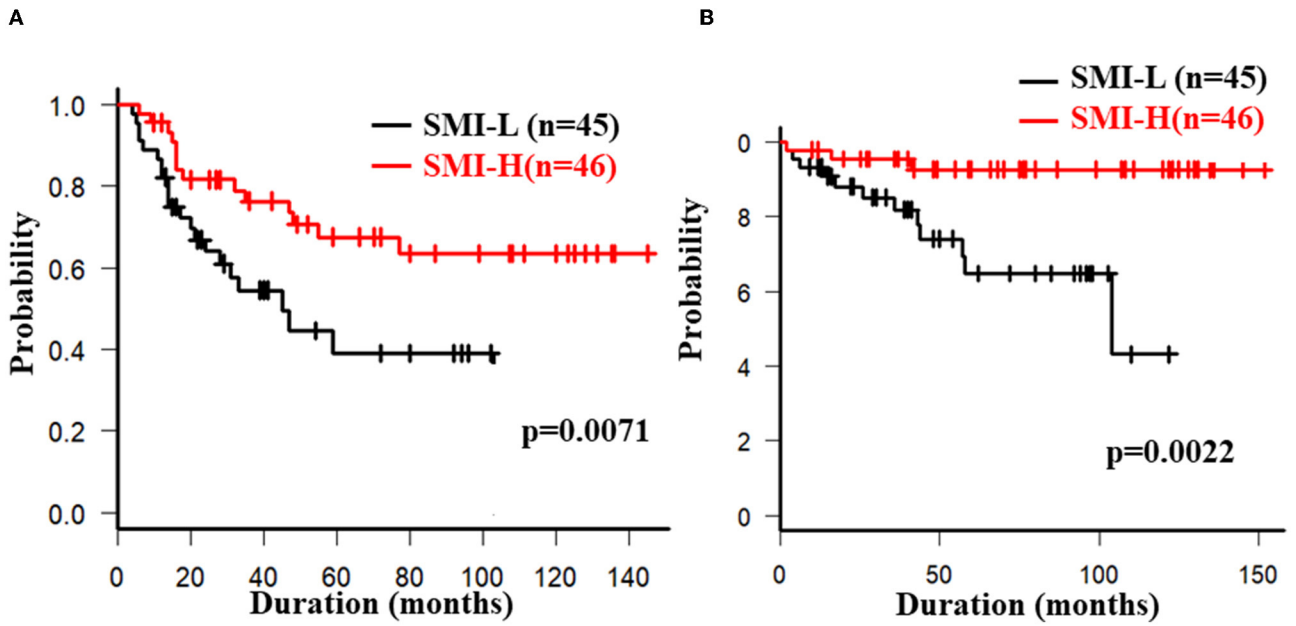

FIGURE 1 | Cumulative secondary failure-free **(A)** and bowel resection-free **(B)** rates classified according to the SMI.

visceral and subcutaneous fat areas did not differ to a statistically significant extent despite a higher tendency in males. The cut-off value of SMI was established as sex-specific because sex-specific cut-off values of skeletal muscle areas have commonly been used for certain investigations.

Cut-Off Values Based on ROC Analysis

ROC analyses were performed to determine cut-off values for secondary failure of anti-TNF-α antibody therapy. The cut-off values were determined based on the threshold nearest to the top-left corner of the ROC curve, and were as follows: age at the induction of anti-TNF-α, threshold 32, AUC 0.6907; BW, 56.3, AUC 0.5916; BMI, threshold 19.0; AUC 0.661; AC, threshold 71.2, AUC 0.616; duration of disease, threshold 180.0, AUC 0.576; disease duration until the induction of anti-TNF-α antibody therapy, threshold 49, AUC 0.569; WBC, threshold 6060, AUC 0.532; TLC, threshold 1030, AUC 0.492; serum Alb, threshold 3.4, AUC 0.579; TC, threshold 125, AUC 0.540; CRP, threshold 3.22, AUC 0.492; VFA, threshold 50.8, AUC 0.603; SFA, threshold 50.8, AUC 0.438; MFI, threshold 0.77, AUC 0.554; SMI, threshold of males 43.2, threshold of females 31.0, AUC of males 0.547, threshold of females 0.650, male; and SMA/SF, threshold 2.2, AUC 0.457.

Comparison of Cumulative Secondary Failure-Free and Bowel Resection-Free Rates Classified According to Body Composition Measurements

The overall 5-year cumulative secondary failure-free and bowel resection-free rates after the induction of anti-TNF therapy were 55.0% and 80.4%, respectively (**Supplementary Figures 1A,B**). The 5-year cumulative secondary failure-free and bowel resection-free rates in patients with a low SMI were 39.1 and 64.8%, respectively, which were significantly lower than those in patients with a high SMI (67.5% and 92.7%; $p = 0.0071$ and 0.0022, respectively) (**Figures 1A,B**). The 5-year cumulative secondary failure-free rate in patients with low VF (45.0%) was lower than that in patients with high VF (77.6%; $p = 0.016$), and the 5-year bowel resection-free rate in patients with low VF (74.5%) tended to be low in comparison to that in patients with high VF (91.8%; $p = 0.13$) (**Figures 2A,B**). The 5- year cumulative secondary failure-free rate and bowel resection-free rates were not affected by SFA (**Figures 2C,D**). The 5-year bowel resection-free rate in patients with a high MFI (68.9%) was significantly lower than that in patients with a low MFI (83.0%; $p = 0.031$), while the 5-year secondary failure-free rates in two groups did not differ to a statistically significant extent difference (**Figures 3A,B**). When classified into four groups based on the combination of low-and high- SMI and VF, the 5-year cumulative secondary failure-free rate in the high SMI and high VF group was 77.0%, which tended to be high in comparison to the other three groups. Additionally, the 5-year cumulative bowel resection-free rate in the low SMI and low VF group (51.3%) was significantly lower than that in the high SMI and low VF group (92.0%; $p = 0.027$) (**Supplementary Figures 2A,B**).

Comparison of Cumulative Secondary Failure-Free and Bowel Resection-Free Rates With Other Measurements and Patient Characteristics

The 5-year cumulative secondary failure-free and bowel resection-free rates in patients who were <32 years of age at

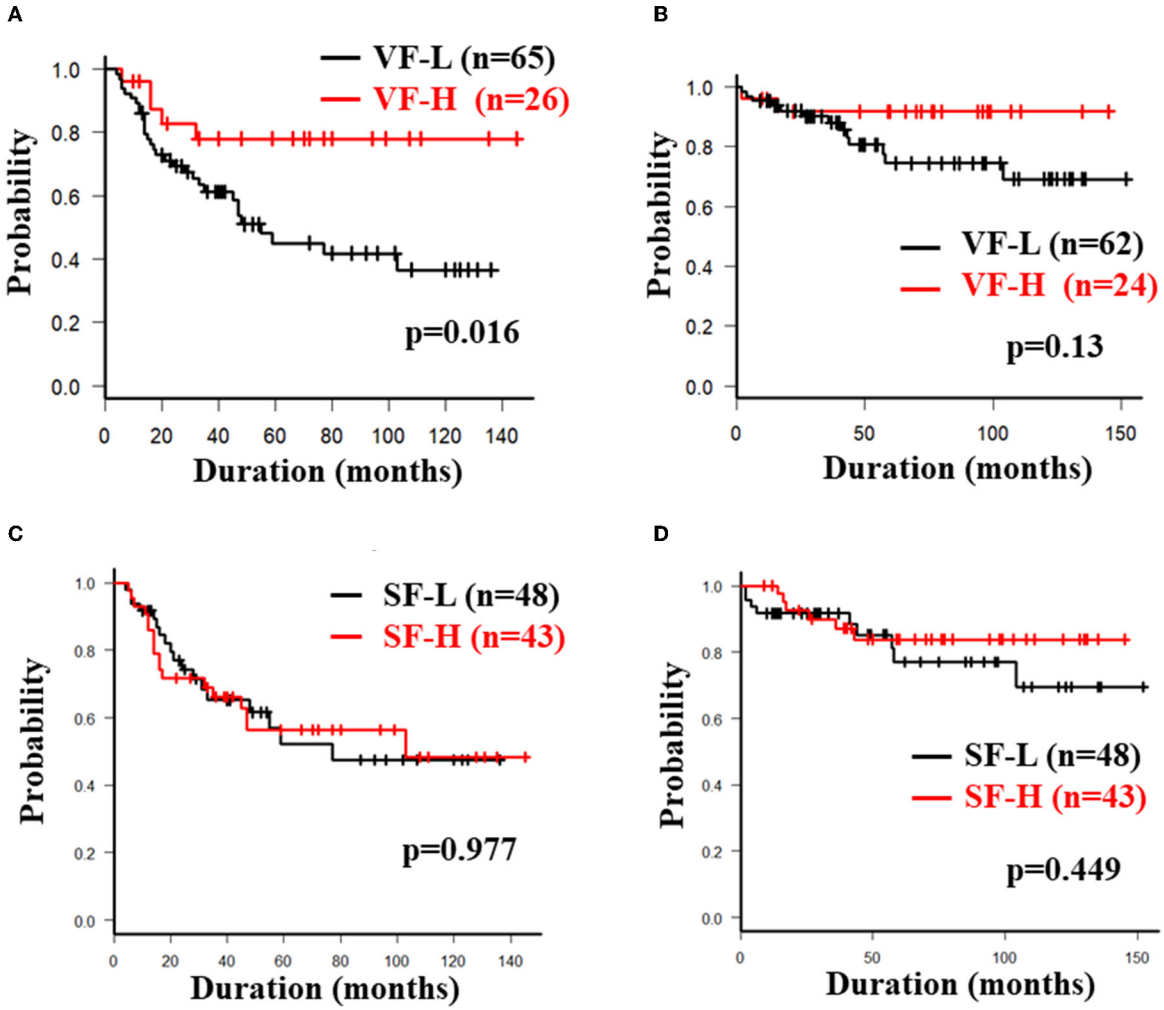

FIGURE 2 | Cumulative secondary failure-free and bowel resection-free rate classified according to the fat mass. Each figure shows the cumulative secondary failure-free rate **(A)** and bowel resection-free rate **(B)** classified according to VF, and the cumulative secondary failure-free rate **(C)** and bowel resection-free rate **(D)** classified according to SF.

the induction of anti-TNF-α antibody therapy were 37.4% and 71.2%, respectively, which were significantly lower in comparison to those who were ≥32 years of age (70.7% and 88.9%; $p = 0.0083$ and 0.027, respectively) (**Figures 4A,B**). The 5-year bowel resection-free rate in patients whose body weight (BW) was <56.3 kg at the induction of anti-TNF-α antibody therapy was 71.0%, which was significantly lower in comparison to that in patients whose BW was ≥56.3 kg (91.3%; $p = 0.020$) (**Figures 4C,D**). The 5-year cumulative secondary failure-free and bowel resection-free rates in patients with BMI <19.0 at the induction of anti-TNF-α antibody therapy were 27.2 and 64.8%, respectively, which were significantly lower than those in patients with BMI ≥19.0 (68.3% and 87.9%; $p = 0.014$ and 0.030, respectively) (**Figures 4E,F**). No other characteristics or measurements affected the 5-year cumulative secondary failure-free or bowel resection-free rates (**Tables 2A**, **3A**).

The Risk Factors According to the Multivariate Analysis

In a multivariate analysis with a Cox proportional hazards model, low SMI (hazard ratio 2.15, 95% confidence interval 1.04-4.44, $p = 0.039$) was the only independent risk factor for secondary failure. A low SMI was also detected as an independent risk factor for bowel resection (hazard ratio 4.19, 95% confidence interval 1.01–17.3, $p = 0.048$), suggesting that its useful as a marker for predicting the long-term outcomes in CD patients treated with anti-TNF-α therapy. Age <32 years at the induction of anti-TNF-α antibody therapy (hazard ratio 4.06, 95% confidence interval 1.07–15.4, $p = 0.039$) and MFI>0.77 (hazard ratio 4.31,

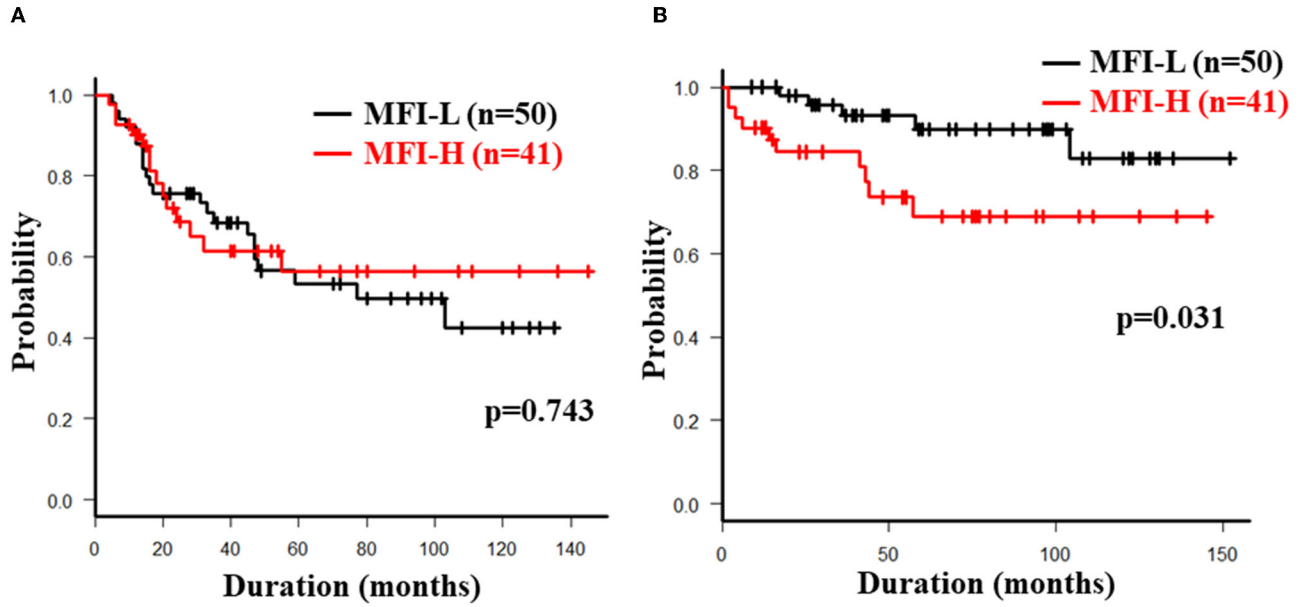

FIGURE 3 | Cumulative secondary failure-free **(A)** and bowel resection-free **(B)** rates classified according to the MFI.

95% confidence interval 1.36–13.7, $p = 0.013$) were detected as independent risk factors for bowel resection (**Tables 2B**, **3B**).

DISCUSSION

This is the first report to elucidate the correlation between altered body composition (skeletal muscle, visceral fat mass and distribution of visceral and subcutaneous fat) and long-term outcomes (need for surgery as well as secondary failure) over 5 years after anti-TNF therapy in anti-TNF-naïve CD. Our multivariate analysis clearly indicated that a low SMI was associated with a low cumulative secondary failure-free rate and bowel resection free-rate after anti-TNF therapy. A significant difference was observed in the SMI values of male and female patients in our study. Therefore, the sex-specific cut-off values for the SMI were established in our study. In addition to the present study, sex-specific cut-off values have commonly been used for the SMI in other studies. In the Cox proportional model that included sex, a low SMI was still identified as an independent risk factor for both secondary failure (HR 2.16, 95% CI 1.02-4.60, $p = 0.044$) and bowel resection (HR 2.18, 95%CI 1.03-4.65, $p = 0.043$). We therefore concluded that a low SMI was an independent risk factor, irrespective of sex.

Very few studies have shown the relationship between the status of skeletal muscle and the outcomes of CD patients treated with anti-TNF therapy. Ding et al. showed that the presence of myopenia was an independent predictor of a primary non-response to anti-TNF therapy in CD (7). Holt et al. proposed that low muscle mass at the initiation of anti-TNF therapy for IBD was identified as a risk factor for a secondary loss of response to anti-TNF therapy while the average observational period was approximately 2 years and the surgery rate was not mentioned (31). Considering our results and previous reports, a low SMI before the initiation of anti-TNF therapy is a useful predictive marker of the long-term outcomes associated with primary and secondary loss of response and the need for abdominal surgery. Interestingly, the previous report suggested that the trough level of adalimumab was negatively correlated with the body surface area and muscle parameters, although the study population was relatively small (32). The trough levels of anti-TNF-α antibodies and neutralizing antibodies to anti-TNF-α antibodies have been known to be associated with a secondary loss of response to anti-TNF-α antibodies. Further studies are required to elucidate the correlation among these parameters, body composition, and outcomes.

Previous studies have suggested that, under chronic inflammation, a decreasing level of IGF-1 caused by TNF-α and IL-6, an increasing level of myostatin, known as myokine, secreted from skeletal muscle and proinflammatory cytokines, including TNF-α itself, reduced muscle synthesis and enhanced muscle degradation (4). Indeed, Subramaniam et al. reported that anti-TNF therapy reverses sarcopenia in patients with CD (33). This suggests that inflammation- and muscle-associated mediators altered by chronic inflammation, including CD mediate the reduction of skeletal muscles. Notably, a myokine, irisin, has been reported to ameliorate experimental colitis and reduce the colonic TNF-α concentration (34), suggesting that the skeletal muscle condition is a new treatment target for CD, as well as a predictive marker of the effect of anti-TNF therapy. Further investigation concerning the interaction between skeletal muscle and chronic inflammation, particularly the influence of muscle- and inflammation-associated mediators, is needed to

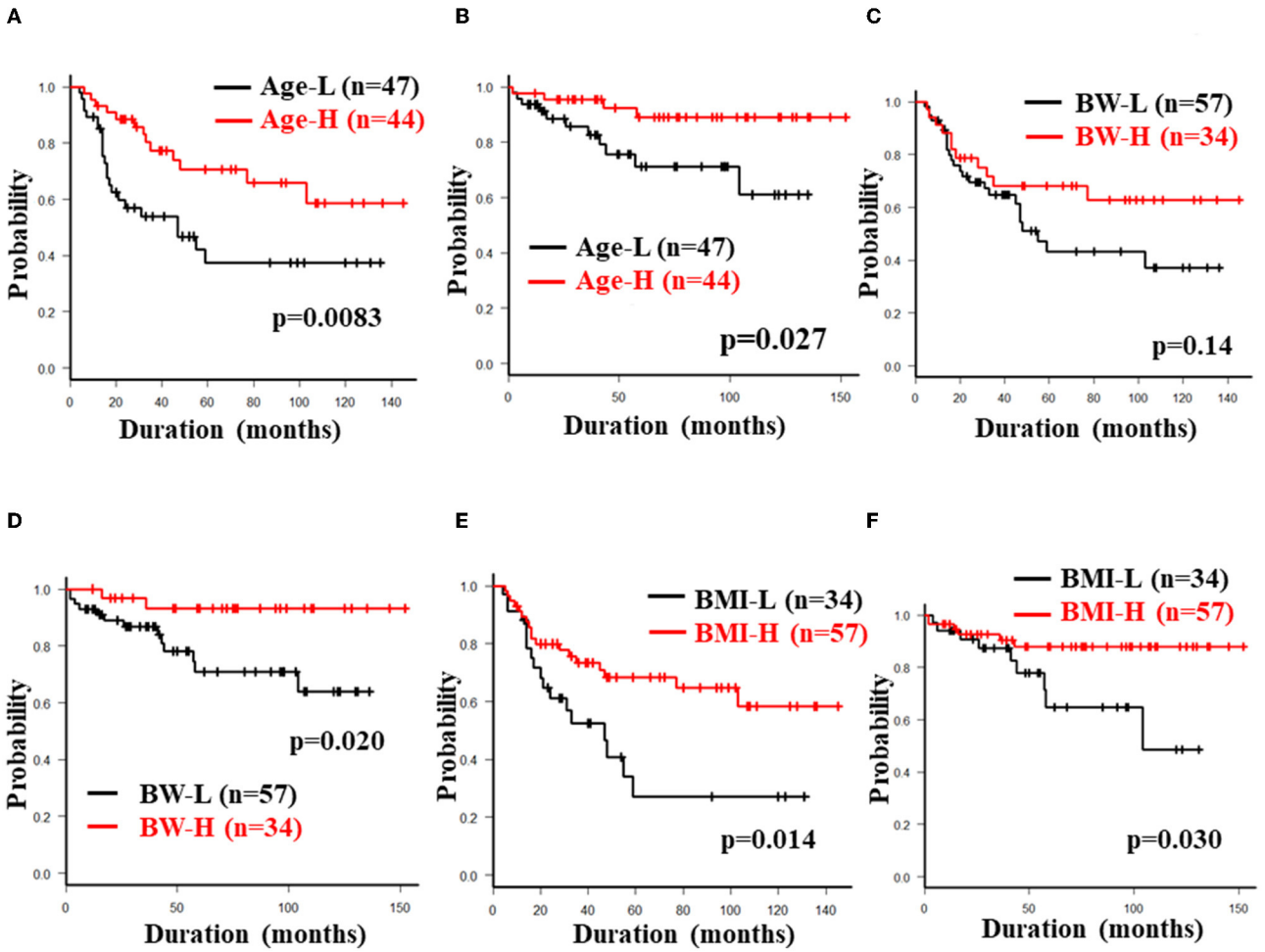

FIGURE 4 | Cumulative secondary failure-free and bowel resection-free rates classified according to age at induction, BW and BMI. The figures show the cumulative secondary failure-free rate **(A)** and bowel resection-free rate **(B)** classified according to the age at induction, the cumulative secondary failure-free rate **(C)** and bowel resection-free rate **(D)** classified according to BW, and the cumulative secondary failure-free rate **(E)** and bowel resection-free rate **(F)** classified according to BMI.

elucidate the pathophysiology as well as novel biomarkers and treatment targets in CD.

Our univariate analysis demonstrated that the cumulative secondary failure-free and bowel resection-free rates were higher in CD with a low absolute volume of VF. However, in our multivariate analysis, VF was not reported to be an independent risk factor for the clinical outcomes, while the MFI, which reflected the fat distribution, was detected. These results suggest that the fat distribution is more important than the absolute volume of visceral and subcutaneous fat for predicting the response to anti-TNF therapy. The findings of most previous reports concerning absolute visceral fat and disease activity and the outcomes of CD conflicted with our results (9, 15, 35, 36). Only one report showed that lower visceral fat in CD predicted an increasing rate of surgery or mortality (12). This discrepancy between our results and previous studies was considered due to the diversity of the absolute VF volume in the patients of each study. For example, Shen et al. reported in another Asian study that a low VFA was associated with mucosal healing after anti-TNF therapy and good clinical outcomes. However, the average VFA in the low VFA group (47.7 cm^2) was almost the same as that of the high VFA group in our study (48.6 cm^2). Furthermore, the average VFA of the high VFA group in the study of Shen et al. was much higher than that of the high VFA group in our study (35). In addition, according to studies from Western countries (15), the average VFA in enrolled CD patients was much higher than that in our study and other Asian studies. These data indicated that the absolute volume of VF was dependent on the patient background factors, including region, race and dietary habits (37). Infliximab clearance was found to be increased in IBD patients with high (>120 kg) and low (<40 kg) body weight (38), which suggests that an appropriate volume of VF maintained the proper concentration of anti-TNF antibody in CD patients. In a previous study analyzing the correlation between the MFI and disease behavior, the MFI in complicated CD (fistulating and stricturing type) was significantly higher than

TABLE 2A | Univariate analyses of factors associated with secondary failure during anti-TNF therapy (log rank test).

	5-year cumulative secondary failure-free rate	*p*-value
Age at induction of anti-TNF-α antibody <32 years	37.4%	0.0083
≥32 years	70.7%	
Male	57.0%	0.85
Female	44.9%	
Body weight <56.3 kg	43.3%	0.14
≥56.3kg	68.0%	
BMI <19.0 kg/m^2	27.2%	0.014
≥19.0 kg/m^2	68.3%	
AC <70.6 cm	42.4%	0.22
≥70.6 cm	63.5%	
Disease background at induction of anti-TNF-α antibody therapy		
Type of disease (I/IC/C)	60.6%/50.4%/57.8%	0.89
Duration of disease <180 months	54.1%	0.39
≥180 months	55.0%	
Duration until the induction of anti-TNF-α antibody therapy <49 months	37.4%	0.96
≥49 months	70.7%	
Type of anti-TNF-α antibody therapy - Infliximab	57.3%	0.61
-Adalimumab	43.3%	
Concomitant immunomodulator usage: Yes	74.0%	0.11
No	46.4%	
Laboratory data before the induction of anti-TNF-α antibody		
WBC <6060/μl	59.2%	0.14
≥6060/μl	53.8%	
TLC<1030/μl	54.2%	0.69
≥1030/μl	61.8%	
Serum Alb <3.4 g/dl	54.1%	0.91
≥3.4 g/dl	62.2%	
T-Chol <125 mg/dl	57.5%	0.72
≥125mg/dl	57.7%	
CRP <3.2 mg/dl	57.5%	0.26
≥3.2mg/dl	58.3%	
Body composition parameters		
VFA <50.8 cm^2	45.0%	0.016
≥50.8	77.9%	
SFA <50.8 cm^2	52.1%	0.977
≥50.8 cm^2	56.3%	
MFI >0.77	53.4%	0.743
≥0.77	56.3%	
SMI <43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)	39.1%	0.0071
≥43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)	67.5%	
SMA/SFA <2.2	51.7%	0.518
≥2.2	57.8%	

BMI, Body mass index; AC, Abdominal circumference; I/IC/C, Ileitis/Ileo-colitis/Colitis; WBC, White blood cell count; TLC, Total lymphocyte count; Alb, Albumin; T-Chol, Total cholesterol; CRP, C-reactive protein; VFA, Visceral fat area; SFA, Subcutaneous fat area; MFI, Mesenteric fat index; SMA, Skeletal muscle area; SMI, Skeletal muscle index.

TABLE 2B | Multivariate analyses of factors associated with secondary failure during anti-TNF therapy (Cox proportional hazards analysis).

	Multivariate analysis		
	HR	**95% CI**	***p* value**
Younger age (Age at the induction of anti-TNF-α antibody <32 years)	1.93	0.93–3.97	0.076
Low BMI (BMI <19.0 kg/m^2)	1.18	0.56–2.51	0.65
Low VFA (VFA <50.8 cm^2)	1.92	0.67–5.49	0.23
Low SMI [SMI <43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)]	2.15	1.04–4.44	0.039

that in uncomplicated CD and the MFI was only an independent predictor of complicated behavior of CD; accordingly it was reported to be a possible predictive marker for aggressive CD (8). Furthermore, a high proportion of visceral fat to total fat mass, which indicated a high proportion of visceral to subcutaneous fat, has been reported to be associated with an increasing level of proinflammatory cytokine and disease activity (9). Thus, the MFI has been suggested to be affected with natural history of CD. Our study reported that CD in the high MFI group was a predictive factor for bowel resection while a high absolute VF value in CD was a negative predictive factor for the long-term prognosis. This discrepancy emphasizes the importance of fat distribution. Further studies are needed to determine the appropriate range of the absolute VF volume and MFI in individual patients.

Mesenteric adipocytes have been known to release adipokines, such as leptin and adiponectin, and proinflammatory cytokines such as TNF-α, IL-6 and IL-1β (39). Previous research revealed that excessive mesenteric fat in CD exacerbated intestinal inflammation via an imbalance of adipokine, increasing the levels of proinflammatory cytokines and macrophage infiltration (39). Additionally, crosstalk between adipokine-releasing adipocytes and myokine-releasing skeletal muscle have been reported in experimental colitis model (40). The role of skeletal muscle and adipocytes in the pathophysiology of CD needs to be elucidated and the new biomarkers and therapeutic targets most be identified.

In our study, young age (<32 years) at the induction of anti-TNF therapy was a positive predictive factor for bowel resection in multivariate analyses. A meta-analysis by Zhang et al. suggested that younger age at the onset of CD was a predictor of an LOR to infliximab (41). Patients in whom anti-TNF therapy was initiated at a young age were thought to have severe inflammation. Additionally, younger age was reported to be an independent risk factor for a non-response to anti-TNF antibody treatment in surgically-treated patients with biologic-naïve stricturing CD (42). These reports indicated that younger age at the onset of CD was a risk factor for primary and secondary failure of anti-TNF therapy.

The present study was associated with some limitations. First, this was a retrospective study with single institutional cohort and a relatively small study population. However, the average

TABLE 3A | Univariate analysis of factors associated with bowel resection during anti-TNF therapy (log rank test).

	5-year cumulative bowel resection-free rate	*p*-value
Age at the induction of anti-TNF-α antibody <32 years	71.2%	0.027
≥32 years	88.9%	
Male	78.1%	0.68
Female	87.5%	
Body weight <56.3 kg	71.0%	0.020
≥56.3kg	93.1%	
BMI <19.0 kg/m^2	64.8%	0.030
≥19.0 kg/m^2	87.9%	
AC <70.6 cm	75.8%	0.71
≥70.6 cm	83.0%	
Disease background at the induction of anti-TNF-α antibody therapy		
Type of disease (I/IC/C)	89.6%/69.0%/85.7%	0.15
Duration of disease <180 months	64.6%	0.28
≥180 months	80.1%	
Duration until the induction of anti-TNF-α antibody therapy <49 months	82.9%	0.80
≥49 months	76.7%	
Type of anti-TNF-α antibody - Infliximab	78.3%	0.35
-Adalimumab	92.8%	
Concomitant immunomodulator usage; Yes	85.6%	0.36
No	72.7%	
Laboratory data before the induction of anti-TNF-α antibody therapy		
WBC <6060 /μl	76.4%	0.89
≥6060 /μl	78.2%	
TLC<1030/μl	76.1%	0.76
≥1030/μl	83.0%	
Serum Alb <3.4 g/dl	79.4%	0.28
≥3.4 g/dl	73.0%	
T-Chol <125 mg/dl	64.1%	0.26
≥125mg/dl	83.3%	
CRP <3.2 mg/dl	76.0%	0.82
≥3.2mg/dl	75.0%	
Body composition parameters		
VFA <50.8 cm^2	91.8%	0.13
≥50.8	74.5%	
SFA <50.8 cm^2	77.1%	0.449
≥50.8 cm^2	83.8%	
MFI >0.77	89.9%	0.031
≥0.77	68.9%	
SMI <43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)	69.4%	0.0022
≥43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)	84.5%	
SMA/SFA <2.2	81.7%	0.88
≥2.2	91.6%	

BMI, Body mass index; AC, Abdominal circumference; I/IC/C, Ileitis/Ileo-colitis/Colitis; WBC, White blood cell count; TLC, Total lymphocyte count; Alb, Albumin; T-Chol, Total cholesterol; CRP, C-reactive protein; VFA, Visceral fat area; SFA, Subcutaneous fat area; MFI, Mesenteric fat index; SMA, Skeletal muscle area; SMI, Skeletal muscle index.

TABLE 3B | Multivariate analysis of factors associated with bowel resection during anti-TNF therapy (Cox proportional hazards analysis).

	Multivariate analysis		
	HR	95% CI	*p* value
Younger age (Age at the induction of anti-TNF-α antibody <32 years)	4.06	1.07–15.4	0.039
Low BW (BW <56.3 kg)	3.63	0.61–21.5	0.16
Low BMI (BMI <19.0 kg/m^2)	0.52	0.13–2.07	0.35
Low MFI (MFI >0.77)	4.31	1.36–13.7	0.013
Low SMI [SMI <43.2 cm^2/m^2 (male), 31.0 cm^2/m^2 (female)]	4.19	1.01–17.3	0.048

observational period in this study was >5 years, which was much longer in comparison to previous studies. Additionally, two different outcomes (secondary failure and bowel resection) were investigated in our study. Furthermore, TNF-naïve CD patients were specifically selected, while previous reports included less specific cohorts, such as hospitalized patients and patients with a history of various medical treatments. Secondly, the cut-off values of the body composition measurements were established with an ROC analysis; thus, therefore, the cut-off values in our study might not be useful in other cohorts, especially Western countries. However, at present, the gold-standard cut-off values of skeletal muscle and fat mass, which might be dependent on region, race and eating habits, have not been established. Further studies are needed to determine the appropriate correction procedures for these measurements to be applied worldwide.

In conclusion, we reported that the skeletal muscle mass, the proportion of visceral fat to subcutaneous fat, and the age at the induction of anti-TNF therapy were associated with long-term clinical outcomes and that they may be helpful as prognostic markers in CD patients who have received anti-TNF therapy. Further investigations are needed to develop appropriate measurements and correction procedures for body composition parameters to be applied in various regions and races, and to determine the mechanisms of interaction between therapeutic responses and the body composition status, particularly through the crosstalk with myokines, adipokines and cytokines, which may contribute to the identification of new biomarkers and molecular targets for CD.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Asahikawa Medical University (Registry Number: 18235). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KA and MF provided major input into the conceptual development of the studies, analyzed the collected data, wrote the manuscript, and supervised all of the investigations. KA, KU, YS, YK, YM, HS, TK, TS, KT, NU, and SK managed and treated the enrolled patients and collected the data. KM, HT, TO, and MF helped design the studies, interpret the data, and prepare/review the manuscript. All of the authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.765209/full#supplementary-material

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The Relationship Between Bone Mineral Density and Body Composition Among Qatari Women With High Rate of Obesity: Qatar Biobank Data

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Studies have reported inconsistent results for the relationship between body composition and bone mineral density (BMD) among women, especially those with a high rate of obesity. This study aims to examine the association between BMD and body composition among Qatari women. A cross-sectional study, using data from the Qatar Biobank (QBB), was conducted on 2,000 Qatari women aged 18 and over. Measurements were taken by dual-energy X-ray absorptiometry (DEXA) for body composition [visceral fat and android fat (AF)], gynoid fat (GF), trunk fat, total fat mass (TFM), total lean mass (LM) and bone mineral density (BMD), including the lumber spine, neck, femur and total body. The participants were divided into groups of normal and low BMD, based on their T-score. Non-linear regression analysis using the restricted cubic spline method was performed according to the T-score of the total BMD for the fat mass variables. Women with a low BMD (T-score <-1) had significantly lower body composition indicators. LM was positively correlated with BMD at the spine ($r = 0.29$, $p < 0.001$), neck ($r = 0.32$, $p < 0.001$), and femur ($r = 0.28$, $p < 0.001$), as well as total BMD ($r = 0.29$, $p < 0.001$) and T-score ($r = 0.31$, $p < 0.001$), while the correlatio between TFM and BMD was negative and weak ($r = -0.05$, <0.017). Results of the non-linear regression indicated that components of fat distribution (TFM, AF, GF and trunk fat) were positively associated with total body T-score. In the adjusted non-liner regression, only a slight increase in T-score was recorded with an increase in FM. The association between FM and BMD was non-linear, suggesting that FM may not be a strong protector of bones among women with high rate of obesity.

Keywords: bone mineral density, body component composition, Qatar, women, abdominal obesity

INTRODUCTION

Bone mineral density (BMD) is the amount of bone mineral content that is measured by dual-energy x-ray absorptiometry (DEXA) in g/cm^2 and is used in the diagnosis of osteoporosis (1, 2). Many factors are known to affect BMD, such as age, sex, vitamin D status (2, 3), the use of certain medications (e.g., glucocorticoids) (4) and obesity (5). Long-term vitamin D deficiency causes a decline in BMD, as a decrease in the levels of vitamin D affects an adequate absorption of calcium. Therefore, bone demineralisation occurs to maintain serum calcium homeostasis (3). According to the 2016–2017 annual report of the Qatar Biobank (QBB) (6), almost 86% of the study population aged 18–65 years, were deficient in vitamin D. The deficiency was found to be higher in women (65%) compared with men (35%), while 70% were obese.

Obesity is one of the modifiable factors associated with BMD (7). Globally, obesity and osteoporosis are both health problems that are closely related to morbidity and mortality (8). Both conditions have been reported due to impaired regulation of the same bone marrow mesenchymal stromal cell (9). In 2016, the prevalence of obesity was higher among women (43.2%) than men (39.5%) in Qatar (10). According to Bener et al. (11), the prevalence of osteoporosis was higher (12.3%) among postmenopausal Qatari women with a high body mass index (BMI) compared with premenopausal women. The association between obesity and BMD is controversial and has not been fully explained (12). Obesity has been reported to be positively associated with BMD (13–15), probably due to the mechanical effect of increased body weight on bone (16), as well as the higher levels of adipose-derived hormones, such as leptin, that promote bone growth (17). On the other hand, some studies have shown that obesity may have a negative effect on BMD (18, 19).

Regarding obesity, it is necessary to consider lean mass (LM) and fat mass (FM), as both of these components of body composition are found to be associated with BMD (20). Several studies have attempted to explain their association with BMD (21–28), although research has provided contradicting findings on the contribution of LM and FM to changes in BMD. Some studies have asserted a positive association between LM and BMD (27, 29), while others (17) found that LM, rather than FM, was the strongest predictor of BMD. In contrast, some studies showed that FM (30) and android /gynoid fat mass ratio (A/G FMR) were positively associated with BMD (22, 31). Nevertheless, other studies reported that both FM and LM have a positive association with BMD (32), while some have observed that the association of FM became negative after adjusting for BMI (15) and weight (23). Additionally, other research has found that FM is negatively correlated to BMD in premenopausal women and positively correlated in postmenopausal women (23, 33).

In view of these inconsistent findings, and the absence of a study in Qatar, this study aims to examine the association between BMD and body composition among Qatari women using data from the QBB.

METHODS

Brief Summary of Qatar Biobank Survey

The QBB is considered to be the first population-based prospective cohort study. Established in 2012, it is partnered with the Ministry of Public Health (MOPH) and the Hamad Medical Corporation (HMC). The QBB continuously gathers biological samples and collects information about the lifestyle and health status of nationals and residents (34).

Study Population

This study included 2,000 samples of Qatari women aged 18 and over, which were selected from the master database of the QBB. Samples were chosen by using a simple random selection method in which each sample had an equal chance of being selected. Excluded samples comprised those from males, pregnant and breastfeeding women and women with chronic diseases, such as hypertension, diabetes mellitus, cancer and chronic kidney disease. Also excluded were women with endocrine diseases (Cushing syndrome, heavy or irregular menses), those following a restrictive diet to lose weight, and women who were using medical treatments with growth hormones. Among the total sample, eight participants were excluded for data missing. The analysis was performed on 1992 participants.

Ethical approval was obtained from the institutional review board of the QBB (EX-2021-QF-QBB-RES-ACC-00040-0166) and was carried out according to the Declaration of Helsinki. All participants in this study provided their written consent to share all their data in research studies, using an identification number but without revealing their identity.

Obesity Indicators, Anthropometric and DXA Derived Parameters

A trained healthcare team at the QBB used standard methods to record the anthropometric measurements. The participants were asked to wear light clothes, without shoes, when measurements were being taking for height and weight. The measurements included those for weight, height, waist circumference (WC) and hip circumference (HC).

Body weight (kg) and height (cm) were measured by using a calibrated scale and a wall-mounted stadiometer (Seca, Hamburg, Germany).Using a non-stretchable tape, WC (cm) was determined at the abdominal region, at the level of the umbilicus at the midpoint between the last rib of the body and the top of the iliac crest. Waist to hip ratio (WHR) was also calculated. Overall adiposity, total body fat (TBF), visceral fat, and regional fat distribution (trunk, AF and GF) and BMD were measured using Lunar iDXA (SN 210520, GE Healthcare, USA). For BMD, three regions of interest were measured on the GE Lunar iDXA machine—the anteroposterior (AP) lumbar spine, the left femur and the whole-body composition. The Lunar iDXA performed a daily six-point calibration which provided highly sensitive measurements with normal, osteopenic and osteoporotic BMD values, as well as lean, normal and obese values (34).

Central obesity was determined by using WC, defined as WC ≥102 cm for men, and WC ≥88 cm for women. BMI was calculated using weight (kg) over the square height in meters (m) (35). Therefore, overweight (OW) was defined as BMI = 25–29.9 kg/m^2 and obesity (OB1) as BMI = 30–34.9 kg/m^2; (OB2) as BMI= 35–39.9 kg/m^2 and (OB3) BMI >40 kg/m^2. Measurements were obtained by Lunar iDXA (SN 210520, GE Healthcare, USA) BMD indicators in the lumbar spine, femoral neck (FN), femur and total BMD, and the total body T-score (Difference in the BMD between participant and a healthy young adult). The results of the BMD measurements were expressed in g/cm^2.

Covariates

Self-administered health and lifestyle questionnaires were used to obtain data such as age, level of education, smoking status and physical activity. The level of education was divided into three categories—lower education, up to secondary school; medium, technical or professional school; and higher education, University and above. The physical activity levels were expressed as metabolic equivalents (METs) in hours per week were calculated based on the frequency and duration of the different types of physical activity Face-to-face interviews were conducted at the QBB clinic by professional nurses, to gather information about health status, related family medical history and usage of medications of participants.

Statistical Analysis

The data was analyzed using SPSS for Windows (version 23) and STATA (version 17), and the results were presented as mean and standard deviations (SD) for continuous variables and as percentages for categorical variables. The participants were categorized into two groups, normal and low BMD, based on the z-score for total body BMD (T-score >-0.99, normal BMD; T-score <-1, low BMD) as per criteria from the World Health Organization (36). A comparison between the groups was made using a *t*-test for continuous variables and a chi-square test (χ^2) for categorical variables. The non-linear association between different types of FM indicators and the T-score of total BMD was assessed by the restricted cubic spline method, with models adjusted for age, smoking, physical activity and the use of supplements. Three knots were put at the 10, 50, and 90th percentile. A *p*-value for non-linearity was obtained by testing the regression coefficient of the second spline equal to zero, while the overall *p*-value for the association was obtained by testing the regression coefficient of the two splines simultaneously equal to zero. The results were visually presented, and the statistical significance for analysis was detected at $p < 0.05$.

RESULTS

Sample Characteristics

Characteristics of the participants categorized according to their z-scores of the total BMD are presented in **Table 1**. The mean age of the participants was 51.55 ± 8.01 years. Compared with participants in the low BMD category, those in the normal BMD category were younger ($p < 0.001$). Most of the participants had obtained higher education (40.1%), and there was no significant difference in levels of education between those in the normal and low BMD groups. More than half of the participants were using vitamin supplements (51.1%), and there was no significant difference in the number of vitamin supplement users among the two categories.

TABLE 1 | Characteristics of the study population according to BMD category[a].

Demographics	Normal BMD (z-score >-0.99) *n* = 1,649	Low BMD (z-score <-1) *n* = 343	Total *n* = 1992
Age, years	50.91 ± 7.6	54.52*** ± 9.16	51.6 ± 8.0
Education level, *n* (%)[b]	628 (38.1)	144 (42.0)	772 (38.7)
Lower education[c]			
Medium education[d]	357 (21.6)	65 (19.0)	422 (21.2)
Higher education[e]	664 (40.3)	134 (39.1)	798 (40.1)
Vitamin Supplement use, *n* (%)[f]	508 (51.3)	104 (50.2)	612 (51.1)

[a]*Values are expressed as mean ± SD for continuous variables and n (%) for categorical variables. Independent t-tests were used for continuous variable and λ^2 tests for categorical variables. Significant P-values are indicated by ***p < 0.001. BMD, bone mineral density.* [b]$\lambda^2 = 2.192$, $p = 0.334$. [c]*Education up to secondary school.* [d]*Technical or professional school.* [e]*University and above.* [f]$\lambda^2 = 0.288$, $p = 0.866$.

Anthropometric Measurements

The anthropometric measurements according to BMD category are shown in **Table 2**. Participants with a normal BMD were heavier and had a high BMI, WC and HC. There was a significant difference between those with normal and low BMD in body composition indicators (visceral FM, android FM, gynoid FM, trunk FM, total FM and total LM), with high values among the normal BMD categories. Those who were OW accounted for 38.8% of the participants, with a high prevalence among those with a low BMD (47.1%). More than half of the participants were obese (51.5%), and the prevalence of obesity 1, 2 and 3 was 10.3, 27.1, and 14.1%, respectively. There was a significant difference in the prevalence of obesity 2 and obesity 3 among the participants, with a higher proportion among the normal BMD category, 29.9 and 16.1%, respectively. However, there was no significant difference in the prevalence of obesity 1 among those with a normal BMD (10.3%) and low BMD (10.2%).

Association Between Bone Mineral Indicators and Body Composition Indicators

The partial correlation between indicators for bone mineral and body composition is shown in **Table 3**. Visceral FM (0.09; $p < 0.001$) and trunk FM (0.06; $p = 0.009$) were positively correlated with spine BMD. On the other hand, gynoid FM (−0.06; $p = 0.008$) was negatively correlated with spine BMD. All FM variables did not show a significant association with femoral neck (FN) BMD. A significant negative correlation with femur BMD was observed for gynoid FM (−0.13; $p < 0.001$) and total FM (−0.10; $p < 0.001$). In contrast, visceral FM (0.08; $p < 0.001$) showed a positive correlation with femur BMD. Additionally, android FM (−0.05; $p = 0.038$) and total FM (−0.05; $p = 0.017$)

TABLE 2 | Anthropometric measurements according to BMD category[a].

Anthropometric measurements	Normal BMD (z-score >-0.99) *n* = 1,649	Low BMD (z-score <-1) *n* = 343	Total *n* = 1,992
Height (cm)	156.72*** ± 5.76	154.70± 6.29	156.37 ± 5.90
Weight (Kg)	81.23*** ± 14.34	71.54 ± 14.78	79.56 ± 14.89
BMI (Kg/m^2)	33.10*** ± 5.73	29.90 ± 5.86	32.55 ± 5.87
WC (cm)	92.61*** ± 11.71	87.33 ± 12.41	91.69 ± 11.99
HC (cm)	112.44*** ± 11.04	106.95± 11.65	111.49 ± 11.33
WHR	0.82 ± 0.08	0.82 ± 0.09	0.82 ± 0.08
Visceral FM (g)	1,075.67*** ± 530.55	884.89 ± 491.31	1,042.81 ± 528.84
Android FM (g)	3,170.78*** ± 1,064.49	2,643.77 ± 1,015.79	3,080.63 ± 1,074.57
Gynoid FM (g)	6,219.69*** ± 1,663.11	5,434.56 ± 1,539.08	6,085.39 ± 1,668.55
Trunk FM (g)	19,129.25*** ± 5,715.36	16,099.39 ± 5,377.09	18,610.98 ± 5,771.55
Total FM (g)	38,070.24*** ± 9,921.97	32,866.83 ± 9,544.59	37,180.18 ± 10,049.04
Total LM (g)	40,370.52*** ± 5,388.08	35,949.42 ± 5,068.78	39,614.28 ± 5,587.48
BMI categories, *n* (%)[b]			
UW	0 (0)	2 (0.6)	2 (0.1)
NW	81 (4.9)	58 (16.9)	139 (7)
OW	436 (26.4)	130 (37.9)	566 (28.4)
OB 1	593 (36)	95 (27.7)	688 (34.5)
OB 2	351 (21.3)	42 (12.2)	393 (19.7)
OB 3	188 (11.4)	16 (4.7)	204 (10.2)

[a]*Values are expressed as mean ± SD for continuous variables and n (%) for categorical variables. Independent t-tests were used for continuous variable and* λ^2 *tests for categorical variables. Significant P-values are indicated by* ***$p < 0.001$. *WC, Waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; FM, Fat mass; LM, Lean mass; UW, Underweight; NW, Normal weight; OW, Overweight; OB 1, Obese type 1; OB 2, Obese type 2; OB 3, Obese type 3.* [b]$\lambda^2 = 111.3$, $p < 0.01$.

were negatively associated with total BMD. A negative correlation was found between total BMD T-score and gynoid FM (−0.10; $p < 0.001$) and total FM (−0.08; $p < 0.001$). Compared with other body composition variables, total LM had a significantly higher positive association with all bone mineral indicators.

Association Between FM Variables and T-Score

The association between the T-score of the total BMD and components of fat distribution (total FM, android FM, gynoid FM, and trunk FM) are illustrated in **Figure 1**. The model was adjusted for age, physical activity, supplement use and smoking status. The fat distribution components exhibited a significant, non-linear relationship with the T-score ($p < 0.001$). In the graph of total FM, the line was not as steep after the total FM reached 40 kg. For android FM, the approximate threshold value was 4 kg and the increase in the T-score was not as steady for values above the threshold. The approximate threshold value for gynoid FM was 6 kg, and when the gynoid FM was below 6 kg, the T-score showed a small linear increase. In contrast, the association with T-score became weaker and the line approached a plateau for the gynoid FM >6 kg. In the trunk FM graph, the approximate threshold value was 20 kg, and the line was not as steep when the trunk FM was above 20 kg.

DISCUSSION

This population-based cross-sectional study evaluated the association between body composition and BMD indicators in Qatari women (≥18 years) based on recent data from the QBB that was obtained in August 2021. To the best of this research group's knowledge, this was the first study to demonstrate the relationship between fat distribution and BMD among Qatari women. The prevalence of obesity in this study population was higher (51.5%) compared with results from the Qatar health report 2014–2016, where the prevalence of obesity in women was 43.2% (10). This rate of increase is consistent with the fact that the prevalence of obesity in Qatar is increasing (18). Compared with FM, a strong positive association was found between LM and BMD at different sites (lumbar spine, femur, and FN), as well as with total BMD and the T-score of total BMD. The association between fat distribution variables and the T-score of total BMD resulted in a significant non-linear curve.

According to this study, those with obesity had a higher BMD, which was consistent with the study by Salamat et al. (15), where obese premenopausal and postmenopausal women (BMI ≥25 kg/m^2) had higher BMD compared with those with normal weight (BMI <25 kg/m^2). Similarly, other studies have reported that obesity was positively related to an increased bone mass (13, 14, 16). Qiao et al. (16) stated that a possible reason for the positive association of obesity with BMD was that high body weight contributes to a mechanical loading effect on bone, which enhances the activation of osteoblasts and the formation of bone. In contrast, Gameil et al. (18) showed that among obese Egyptian premenopausal women and those of normal weight, obesity was associated with an increased risk of low BMD. The study revealed a significant inverse relationship ($p < 0.001$) between obesity variables (e.g., BMI) and BMD indicators at different sites (e.g.,

TABLE 3 | Partial correlation between bone mineral indicators and body composition variables[a].

Bone mineral indicators	Visceral FM (g)		Android FM (g)		Gynoid FM (g)		Trunk FM (g)		Total FM (g)		Total LM (g)	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
Spine BMD (g/cm^2)	0.09	**<0.001**	0.01	0.595	−0.06	**0.008**	0.06	**0.009**	−0.02	0.285	0.29	**<0.001**
FN BMD[b] (g/cm^2)	0.03	0.168	−0.003	0.885	−0.003	0.906	0.03	0.130	0.02	0.412	0.32	**<0.001**
Femur[b] BMD (g/cm^2)	0.08	**<0.001**	−0.002	0.913	−0.13	**<0.001**	0.03	0.214	−0.10	**<0.001**	0.28	**<0.001**
Total BMD (g/cm^2)	−0.02	0.345	−0.05	**0.038**	−0.03	0.120	−0.01	0.691	−0.05	**0.017**	0.29	**<0.001**
T-Score[c]	0.04	0.098	−0.02	0.456	−0.10	**<0.001**	0.02	0.446	−0.08	**<0.001**	0.31	**<0.001**

[a] *The correlation model was adjusted for age and BMI. r = correlation coefficient. Bold indicates statistically significant results. FN, Femoral neck.* [b] *Left femur was measured.* [c] *T-score of total BMD.*

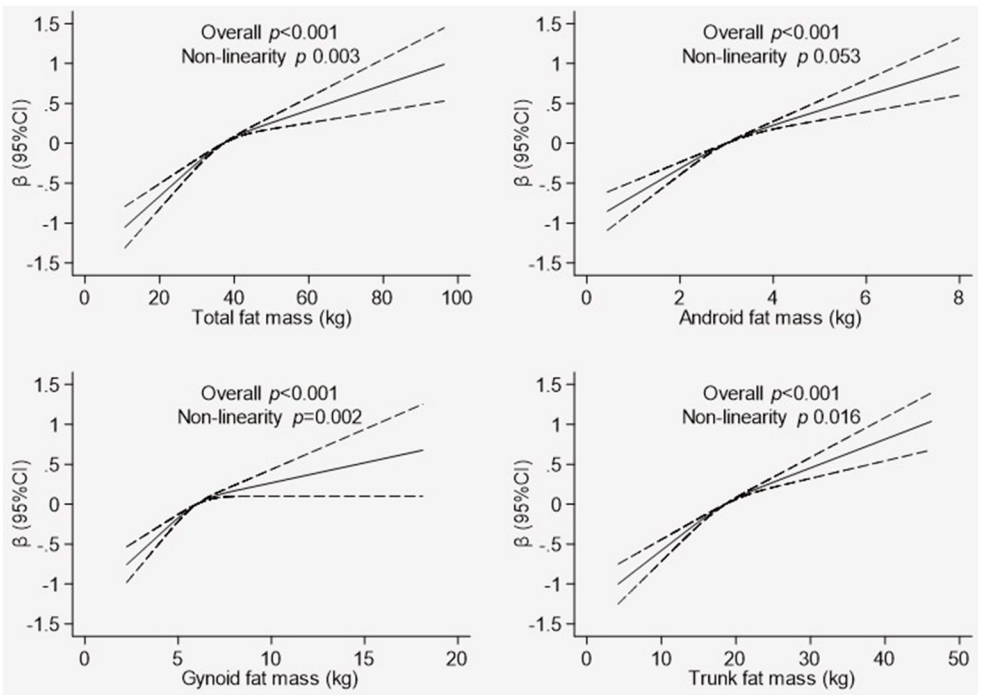

FIGURE 1 | Association between whole body Tscore and body composition indicators. Graphical representation of non-linear association between total fat mass, android fat mass, gynoid fat mass, and trunk fat mass with T-score of total BMD derived using the restricted cubic spline method. The models were adjusted for are age, physical activity, supplement use, and smoking status. Dotted line represents the 95% confidence intervals.

z-score at lumbar spine). Additionally, Beck et al. (37) showed that although heavier individuals have higher hip BMD, women with the highest BMI reported more falls and fractures, and had lower measures of physical activity and function. Therefore, a critical analysis of region-specific BMD should be undertaken.

Age and BMI-adjusted partial correlation indicated that total LM had a significant positive correlation with BMD at different regions, and this agreed with the findings of several other studies (29, 38). A study by Xiao et al. (27) among women (20–95 years), reported that total LM had a greater protective effect on BMD in premenopausal women. They concluded that the effect of LM on BMD could be ascribed to the mechanical influence of muscle, which generates a positive effect on osteogenesis. The findings of this study also indicated that total LM was more positively associated with BMD indicators than the components of fat distribution. Similar findings were observed by Ilesanmi-Oyelere et al. (17) for postmenopausal women. However, Wang et al. (26), in a study of postmenopausal women, found that when adjusted for age, both FM and LM had positive associations with BMD at the lumbar spine, FN and hip regions. This difference in findings might be explained by the association of body composition with bone mass being significantly determined by the parameter of the bone analyzed (39). Additionally, both FM and LM have crucial effects on bone mass, based on the bone parameters used, the site of skeleton where measurements were taken and menopausal status (39).

This study also found that gynoid FM and total FM had a significant negative correlation with BMD at different regions.

Similar findings were reported by Casale et al. (32), where TFM was negatively correlated to BMD among premenopausal women. Conversely, the results were inconsistent with those of Kapuš et al. (22) and Namwongprom et al. (25) among postmenopausal European and Thai women, respectively. This contradiction could be due to the differential effect of FM on bone among postmenopausal and premenopausal women. While this study did not categorize the participants according to their menopausal status, total FM might be a stronger indicator of BMD in postmenopausal rather than premenopausal subjects (38). However, the results of this research agree with those of Salamat et al. (15), which indicated that when BMI was considered as a covariate, the association of TFM with BMD became negative. This negative effect with increased TFM was attributed to the increased levels of cytokines that are proinflammatory. Similarly, Kim et al. (23) found that the association of TFM with BMD among Korean premenopausal women (≥20 years) in weight-adjusted models became negative, which shows that high FM could have a detrimental effect on bone, despite the beneficial effect of mechanical loading.

Furthermore, this study observed a non-linear relationship between the components of fat distribution and the total BMD indicator (T-score), where the slope was not as steep as the TFM increased. An increased TFM might not have a protective effect on bone. This finding was comparable with the conclusions of Shi et al. (31) in a study of Chinese postmenopausal women. They explained that TFM has a curved association with bone indicators, and a strong protective influence of TFM on bone occurs only in thin people. For overweight and obese individuals, increased TFM could be damaging to bone health.

Several potential mechanisms have been proposed to clarify the relationship between body composition parameters and bone mineral indicators. The LM could positively affect the bone through muscle contractions, along with the loading effect due to the force of gravity (38), and the advantageous hormonal effect of the skeletal musculature (40). For example, muscle fibers release an insulin-like growth factor 1 (IGF-1) which can trigger the growth of bone via receptors or the signaling mechanism of IGF (41). The effect of TFM on bone is probably more complex, because both bone and adipose cells originate from a pluripotent mesenchymal stem cell (42), and these cells can transform into both adipocytes and osteoblasts (42). The TFM possibly affects the bone positively via the weight-loading mechanism (32), and modulation of the endocrine pathway (38). Adipocytes release a lot of hormones, including leptin, insulin, and adiponectin, that impact bone metabolism (38). Additionally, the adipose tissue contains an aromatase enzyme that changes androgen to estrogen, leading to a high release of estrogen (38). These hormones have a protective effect on bone and results in bone development by initiating osteoblast differentiation and the prevention of resorption by osteoclast. In addition, estrogen enhances the synthesis of protein in muscles and the deposition of bone calcium, leading to an increase in BMD (43). On the other hand, increased adiposity causes inflammation and increased inflammation promotes bone resorption (44). Adipose tissue cells secrete a variety of proinflammatory cytokines, such as interleukin 6 (IL-6) and TNF-α (tumor necrosis factor-alpha). These factors activate bone resorption and inhibit bone formation by the increased stimulation of the receptor activator of nuclear factor-kB ligand (RANKL), which mediates osteoclast formation (45). Furthermore, excessive adiposity also leads to a decrease in the release of the adiponectin hormone which is associated with differentiation of osteoblasts (21). Therefore, excess adiposity causes a decline in BMD.

In diagnosing those with a low bone mass, this study highlighted the importance of considering the impact of fat distribution at different skeletal sites rather than relying on total BMD. This finding has clinical implications as it would be helpful in improving the diagnostic criteria for conditions associated with low bone mass. Future studies could analyse the effect of fat distribution on BMD at different skeletal sites and the variation in the results among obesity categories.

This study had both strengths and limitations. One of the limitations was that a cross-sectional study design prevented the determination of causal association between body composition indicators and BMD. Second, only the total BMD T-score was considered for determining the association of fat distribution with BMD; the BMD at different skeletal sites was not included. Additionally, the study population could have affected the results as they mostly comprised overweight and obese participants. There could also be confounding bias due to residual confounders that were not included in the analysis, such as sex-hormone status, menopausal status, and the levels of bone biomarkers. One of the strengths, however, was that the data obtained from the QBB included a large sample size with anthropometric measurements, body composition variables and bone mineral density indicators.

CONCLUSION

This study illustrates that LM is a stronger predictor of BMD compared with FM. Additionally, it showed that FM might not have a strong protective effect on bone health as the association of FM with T-score was non-linear and there was not much increase in the T-score when FM increased. Further investigations are necessary to confirm the association between FM and BMD by considering BMD at different regions of the body, as total body BMD might not be a better indicator of bone mass.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to the confidential nature of the material. However, they can be available on request to Qatar Biobank study management team. Requests to access the datasets should be directed to https://www.qatarbiobank.org.qa/.

ETHICS STATEMENT

The studies involving human participants were reviewed and ethical approval was obtained from the Institutional Review Board of the Qatar Biobank (EX-2021-QF-QBB-RES-ACC-00040-0166) and carried out

according to the Declaration of Helsinki. A written consent was obtained for all participants to share their data.

AUTHOR CONTRIBUTIONS

AK and MR conceived and designed the study. SL, YK, TT, and GA contributed to the original draft preparation. AK wrote the manuscript, has full access to all data, and is responsible for the results accuracy. MR and AA critically reviewed data analysis and contributed to the writing and editing of the manuscript. AK and ZS performed the statistical analysis. All authors have read and agreed to the published version of the manuscript.

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The Correlation of Prediabetes and Type 2 Diabetes With Adiposity in Adults

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Background: Fat metabolism is associated with prediabetes and type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the detailed correlation of diabetes status with adiposity among adults.

Methods: Briefly, 28,429 adults aged ≥18 years from both sexes in the National Health and Nutrition Examination Survey (NHANES) 1999–2018 were included in this study. Multivariable linear regression models were used to examine associations of prediabetes and diabetes status, disease duration of T2DM, serum glucose, glycohemoglobin (HbA1c) with total percent fat (TPF), and fat mass distribution.

Results: After adjusting for sociodemographic covariates, health behaviors, hypertension, hypercholesterolemia, there were direct associations of prediabetes and T2DM status with TPF, trunk fat mass, android fat mass, gynoid fat mass and android to gynoid ratio compared with non-diabetes. But the fat mass decreased with the increase of the disease duration in patients with T2DM. Besides, when stratifying by diabetes status, we found direct associations of serum glucose and HbA1c with TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio in non-diabetic and prediabetic participants. But in patients with T2DM, inverse associations of serum glucose and HbA1c with fat mass were observed.

Conclusions: This study indicated that adults with prediabetes and T2DM had significantly higher TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio compared with those without diabetes. Moreover, fat mass decreased as the disease duration increased in patients with T2DM. The associations of serum glucose and HbA1c with TPF and fat mass distribution in patients with T2DM were opposite to the relationships observed in non-diabetic and prediabetic participants.

Keywords: NHANES, diabetes, adiposity, glucose, HbA1c

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INTRODUCTION

Prediabetes, with blood glucose concentrations higher than normal, but lower than the threshold of diabetes mellitus (DM), is a high-risk state of DM development (1). The National Health and Nutrition Examination Survey (NHANES) in 2005–2008 suggested that 35% of the US adults older than 20 years and 50% of those older than 65 years had prediabetes (2). Statistically, 5–10% of people

per year with prediabetes will progress to diabetes (1) and there are more than 425 million diabetics worldwide, which is expected to reach 700 million in 2,045 (3). The causes of this unprecedented rise are the aging population, increasing obesity, physical inactivity, and energy-dense diets (4). Besides, more than 90% of individuals with MD have type 2 diabetes (T2DM) (5), 60% of patients with T2DM are obese (4), and obesity is one of the strongest factors that drive the increase of the incidence of metabolic diseases, including diabetes (6).

Patients with prediabetes or T2DM need to monitor glycohemoglobin (HbA1c) and blood glucose concentration regularly to prevent the development and progression of microvascular and macrovascular complications (4). Compared with body mass index (BMI), total percent fat (TPF) as well as the indexes of fat distribution by region (trunk fat mass, android fat mass, gynoid fat mass and android to gynoid ratio) are more important and accurate indicators in obesity evaluation. Specifically, dual-energy x-ray absorptiometry (DXA) is widely considered a precise and accurate clinical technology for directly measuring fat mass and distribution nowadays (7, 8). In recent years, a significant association between prediabetes or T2DM and adiposity has been established. However, these studies used proxy measures for overall or abdominal obesity such as BMI or waist circumference without taking into account the composition of that mass and the correlation between diabetes status, blood glucose, HbA1c and fat mass measured by DXA in large samples are still limited. Therefore, this study investigated the relationship of diabetes status and disease duration of T2DM with TPF and fat distribution in adults using a nationally representative sample. Furthermore, due to the different blood glucose, HbA1c and adiposity between individuals with and without prediabetes or T2DM, we also evaluated the associations of blood glucose and HbA1c with adiposity in the subgroup stratified by diabetes status.

METHODS

Data Sources

National Health and Nutrition Examination Survey (NHANES) is a continuous surveillance survey conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) to assess the health and nutritional status of the US population. Data obtained from NHANES can be freely available to researchers worldwide. In our study, we pooled data from 10 2-year cycles of NHANES 1999–2018.

Study Population

A total of 101,316 participants were enrolled from the NHANES 1999–2018 database. Among the 59,204 adults aged ≥18 years old, we excluded 28628 participants with incomplete TPF data, 1,763 participants with incomplete serum glucose data, 36 participants with incomplete HbA1c data, and 18 participants who had unclear self-report DM status. To minimize the number of participants with T1DM, 330 participants with age of DM onset before the age of 30 were also excluded. Finally, 28,429 participants were analyzed after applying these exclusion criteria (**Figure 1**).

The National Center for Health Statistics Research Ethics Review Board reviewed and approved NHANES, and all participants signed written consents prior to participating in each year's survey. De-identified data are accessible online.

Study Variables

The outcomes of our study were TPF, trunk fat mass, android fat mass, gynoid fat mass and android to gynoid ratio, which were measured by well-trained technicians using dual energy X-ray absorptiometry (DXA) QDR-4500 Hologic Scanner (Bedford, MA) of the whole body. TPF was calculated by the ratio of total fat mass to total fat and lean mass and multiplied by 100 to produce a percentage. The regions of fat distribution were defined by the Hologic APEX software. Specifically, the trunk fat mass was defined as total fat mass minus fat in limbs and head. The android area was defined as the lower trunk area bounded by two lines: the pelvic horizontal cut line on its lower side, and a line automatically placed above the pelvic line. The upper gynoid line was placed 1.5 times of the height of android region below the pelvic line and the lower gynoid line was placed such that the distance between the two gynoid lines was twice the height of the android region. DXA scans were not performed for participants with a self-reported use of radiographic contrast material (barium) in the last seven days before scans, weight above 450 pounds or height above 192.5 cm.

Exposures were prediabetes and T2DM status, disease duration in those with T2DM, serum glucose and HbA1c. The T2DM status was defined as self-reported physician-diagnosed diabetes (ever told by a doctor that they had DM) or using measures of HbA1c ≥6.5% in those without a self-reported diagnosis, based on the guideline from the American Diabetes Association (9). The prediabetes status was defined as self-reported physician-diagnosed prediabetes (ever told by a doctor that they had prediabetes or borderline DM) or using measures of HbA1c ≥5.7% and ≤6.4% in those without a self-reported diagnosis, based on the guideline from the American Diabetes Association (9). Disease durations in patients with T2DM were defined as the age at screening minus the age when which doctors told the participants they had DM. Serum glucose and Hb1Ac were obtained from the standard biochemistry profile and glycohemoglobin sections in the laboratory data part of NHANES.

Sociodemographic variables mainly included age, sex, race and ratio of family income to poverty threshold. Current insulin use and glucose-lowering medication intake were assessed by questionnaires. Health behaviors variables included smoking status (whether smoked at least 100 cigarettes in life) and vigorous work activity. Health-related variables were hypertension (ever told by a doctor that you have high blood pressure), hypercholesterolemia (ever told by a doctor that you have high cholesterol), BMI and waist circumference (calculated during the study visit). The detailed description of other variables such as total cholesterol, HDL cholesterol, triglyceride, LDL cholesterol as well as blood urea nitrogen, uric acid, creatinine

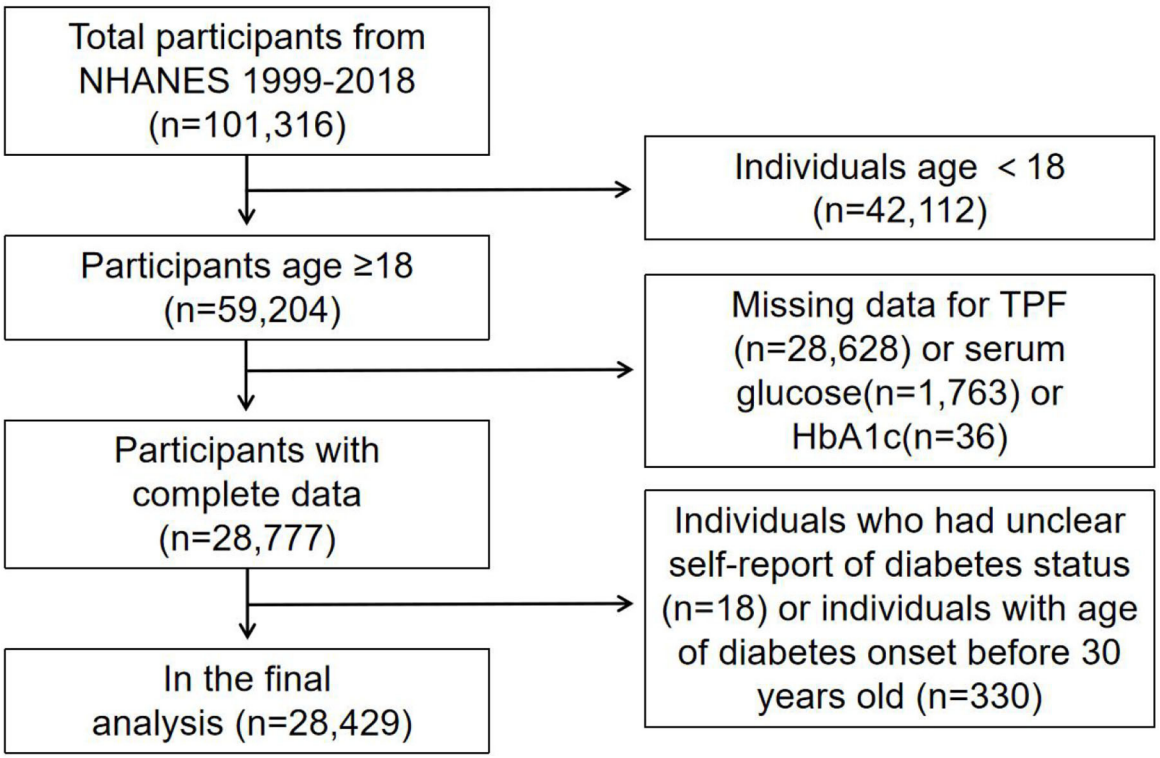

FIGURE 1 | Flow chart of sample selection from the NHANES 1999–2018.

can all be found on the NHANES website (http://www.cdc.gov/nchs/nhanes/).

Statistical Analyses

The NHANES sample weights were used as recommended by the NCHS. All analyses were performed with package R (http://www.Rproject.org) and Empower Stats (http://www.empowerstats.com), p-values <0.05 were considered to indicate statistical significance. The associations between diabetes status, duration of T2DM, serum glucose, HbA1c and TPF or fat distribution were evaluated by multivariable linear regression models. The model was adjusted for age, sex, race, health behaviors (smoking status, vigorous work activity), hypertension, and hypercholesterolemia. Subgroup analyses stratified by sex and diabetes status were also performed.

RESULTS

The weighted distributions of the characteristics according to diabetes status were shown in **Table 1**. In 7,802 prediabetic and T2DM patients, 6,674 (85.5%) participants could be diagnosed as obese based on TPF (men 25%, women >35%), and 3,924 (50.3%) could be diagnosed by BMI ($\geq$30 kg/m^2) (10, 11). Compared with non-diabetic participants, prediabetic, and T2DM participants were older, more had hypertension, hypercholesterolemia, smoked at least 100 cigarettes in life and fewer had vigorous work activity. Besides, prediabetes and T2DM group had higher BMI, waist circumference, total cholesterol, triglyceride, blood urea nitrogen, uric acid, creatinine, and lower ratio of family income to poverty, HDL cholesterol. The mean ± SD of disease duration of diabetes for T2DM group was 6.98 ± 7.97 years and there were 465 patients taking insulin and 1,436 patients taking glucose-lowering medications in all 2,476 patients with T2DM patients. Furthermore, the serum glucose, HbA1c, TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio in adults with prediabetes or T2DM were all higher than non-diabetic participants.

Associations of Diabetes Status With Adiposity

We found the direct associations of prediabetes and T2DM status with TPF and fat distribution compared with non-diabetes in fully adjusted models (βs in sequence of TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio for prediabetes were: 2.12/3032.89/609.47/595.10/0.06; for T2DM they were: 2.49/4937.83/ 944.87/582.69/0.08). The results were all statistically significant with p-values <0.0001. That is to say, after controlling for potential confounding factors, compared with those without DM, the TPF, trunk fat mass, android fat mass, gynoid fat mass and android to gynoid ratio for prediabetes were 2.12%, 3032.89 g, 609.47 g, 595.10 g, 0.06 higher, and for T2DM were 2.49%, 4937.83 g, 944.87 g, 582.69 g, 0.08 higher. In the subgroup analysis stratified by sex, this direct association

TABLE 1 | Weighted characteristics of study samples based on diabetes status.

	Non-diabetes (*n* = 20,627)	**Prediabetes (*n* = 5,326)**	**Diabetes (*n* = 2,476)**	***p*-value**
Sex (%)				0.0155
Males	49.88	48.77	52.76	
Females	50.12	51.23	47.24	
Race (%)				<0.001
Hispanic	14.27	17.66	18.62	
Non-hispanic white	70.44	56.60	56.34	
Non-hispanic black	9.08	17.04	15.85	
Others	6.21	8.69	9.20	
Hypertension (%)				<0.001
Yes	18.17	37.15	58.08	
No	81.83	62.85	41.92	
Hypercholesterolemia (%)				<0.001
Yes	26.11	41.46	58.00	
No	73.89	58.54	42.00	
Vigorous work activity (%)				<0.001
Yes	34.98	24.06	20.58	
No	65.02	75.94	79.42	
Smoking status (%)				<0.001
Yes	44.71	49.00	49.31	
No	55.29	51.00	50.69	
Taking insulin now (*n*)				/
Yes	/	4	465	
No	/	5,199	1,994	
Not available	/	123	17	
Taking pills to lower blood sugar (n)				/
Yes	/	56	1,436	
No	/	946	553	
Not available	/	4,324	487	
Age (years)	39.23 ± 14.39	48.60 ± 13.88	54.45 ± 11.95	<0.001
BMI (kg/m^2)	27.28 ± 5.86	31.29 ± 7.02	33.24 ± 7.35	<0.001
Ratio of family income to poverty	3.03 ± 1.65	2.89 ± 1.63	2.69 ± 1.61	<0.001
Waist circumference (cm)	93.69 ± 14.77	104.09 ± 15.58	110.97 ± 16.45	<0.001
Total cholesterol (mmol/L)	5.01 ± 1.03	5.31 ± 1.10	5.14 ± 1.30	<0.001
Triglyceride (mmol/L)	1.50 ± 1.31	1.97 ± 1.71	2.55 ± 3.16	<0.001
HDL cholesterol (mmol/L)	1.39 ± 0.41	1.27 ± 0.37	1.20 ± 0.34	<0.001
LDL cholesterol (mmol/L)	2.97 ± 0.88	3.25 ± 0.97	2.93 ± 0.98	<0.001
Blood urea nitrogen (mmol/L)	4.51 ± 1.55	4.79 ± 1.72	5.39 ± 2.56	<0.001
Uric acid (umol/L)	313.83 ± 81.65	335.56 ± 80.70	332.01 ± 91.03	<0.001
Creatinine (mmol/L)	75.56 ± 26.79	76.87 ± 29.90	82.16 ± 58.33	<0.001
Serum glucose (mmol/L)	4.94 ± 0.59	5.52 ± 1.22	8.73 ± 4.25	<0.001
Glycohemoglobin (%)	5.19 ± 0.27	5.84 ± 0.49	7.59 ± 1.90	<0.001
Diabetes duration (years)	/	/	6.98 ± 7.97	/
Total percent fat (%)	32.49 ± 8.66	35.98 ± 8.33	36.85 ± 7.82	<0.001
Trunk fat mass (g)	12489.80 ± 5976.04	16369.64 ± 6781.82	18970.05 ± 7352.68	<0.001
Android fat mass (g)	2154.09 ± 1151.41	2890.19 ± 1325.25	3378.72 ± 1420.56	<0.001
Gynoid fat mass (g)	4382.63 ± 1702.18	5006.58 ± 1950.23	4969.78 ± 1934.28	<0.001
Android to gynoid ratio	0.98 ± 0.20	1.07 ± 0.19	1.13 ± 0.18	<0.001

Mean ± SD for continuous variables, p-value was calculated by weighted linear regression model. % for categorical variables, p-value was calculated by weighted chi-square test.

existed in both males and females after adjusting for confounders. These results are presented in **Table 2**.

Associations of Serum Glucose and HbA1c With Adiposity

After adjusting for sociodemographic covariates, health behaviors, hypertension, and hypercholesterolemia, we found direct associations of serum glucose and HbA1c with TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio. And when stratifying by diabetes status, these direct associations still existed in participants without diabetes and with prediabetes. But in patients with T2DM, the correlation of serum glucose with TPF and trunk fat mass, HbA1c with TPF turned to be inverse (serum glucose and TPF: $\beta = -0.10$, 95% *CI*: −0.16∼−0.05; serum glucose and trunk fat mass: $\beta = -79.49$, 95% *CI*: −147.53∼−11.46; HbA1c and TPF: $\beta = -0.13$, 95% *CI*: −0.24∼−0.01). Other associations were of no statistical significance. The results are shown in **Tables 3**, **4**.

Associations of Disease Duration With Adiposity in T2DM

There were inverse associations of disease duration with TPF and gynoid fat mass, which were statistically significant ($\beta = -0.04$, 95% CI: −0.07∼−0.01 and $\beta = -18.41$, 95% CI: −33.91∼−2.91), which could be explained as each unit (1 year) increase in the duration of T2DM, TPF was decreased by 0.04% and gynoid fat mass was decreased by 18.41 g. When stratified by sex, the inverse associations of disease duration with TPF and gynoid fat mass were still statistically significant in females, but not in males. Besides, the inverse associations of disease duration with trunk fat mass, android fat mass and android to gynoid ratio were of no statistical significance either. The results are shown in **Table 5**.

DISCUSSION

The results of our study showed that individuals with prediabetes and T2DM had significantly higher TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio compared with those without DM. The fat mass decreased as the disease duration increased in patients with T2DM. Moreover, in participants without DM and with prediabetes, serum glucose and HbA1c were directly associated with TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio, while the inverse associations were observed in those with T2DM.

Prediabetes and T2DM are associated with the increased insulin resistance in target organs (e.g., liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue) and pancreatic β-cell dysfunction, with nearly 50% cell loss at the diagnosis of T2DM (1, 12). Although patients with prediabetes or T2DM are not necessarily obese, weight gain before DM develop is common (13). Obesity is recognized as the most powerful environmental risk factor among several modifiable risk factors for diabetes (14), which is associated with an increased insulin demand and increased likelihood of insulin resistance leading to prediabetes or hyperinsulinemia and ultimately T2DM (13, 15).

TABLE 2 | Associations of diabetes status with adiposity.

	β (95% *CI*) *p*-value				
	Total percent fat (%)	**Trunk fat mass (g)**	**Android fat mass (g)**	**Gynoid fat mass (g)**	**Android to gynoid ratio**
Total					
Non-diabetes	Reference	Reference	Reference	Reference	Reference
Prediabetes	2.12 (1.91, 2.34) <0.0001	3032.89 (2809.85, 3255.93) <0.0001	609.47 (558.92, 660.03) <0.0001	595.10 (526.20, 664.01) <0.0001	0.06 (0.05, 0.06) <0.0001
Type 2 diabetes	2.49 (2.17, 2.82) <0.0001	4937.83 (4604.11, 5271.56) <0.0001	944.87 (862.59, 1027.14) <0.0001	582.69 (470.77, 694.62) <0.0001	0.08 (0.07, 0.09) <0.0001
Males					
Non-diabetes	Reference	Reference	Reference	Reference	Reference
Prediabetes	2.07 (1.78, 2.36) <0.0001	2472.82 (2177.24, 2768.41) <0.0001	491.17 (420.46, 561.88) <0.0001	457.32 (369.05, 545.60) <0.0001	0.04 (0.03, 0.05) <0.0001
Type 2 diabetes	2.85 (2.43, 3.27) <0.0001	4497.33 (4072.30, 4922.36) <0.0001	785.17 (675.45, 894.90) <0.0001	577.37 (440.82, 713.91) <0.0001	0.04 (0.03, 0.06) <0.0001
Females					
Non-diabetes	Reference	Reference	Reference	Reference	Reference
Prediabetes	2.23 (1.91, 2.55) <0.0001	3619.14 (3289.31, 3948.97) <0.0001	730.95 (659.55, 802.35) <0.0001	743.50 (639.05, 847.95) <0.0001	0.07 (0.06, 0.08) <0.0001
Type 2 diabetes	2.08 (1.59, 2.58) <0.0001	5348.31 (4834.19, 5862.44) <0.0001	1111.89 (989.92, 1233.86) <0.0001	596.94 (418.59, 775.30) <0.0001	0.12 (0.10, 0.13) <0.0001

Age, sex, race, hypertension, hypercholesterolemia, smoking status, and vigorous work activity were adjusted. Sex was not adjusted for in the subgroup analyses.

TABLE 3 | Associations of serum glucose (mmol/L) with adipoity.

	β (95% *CI*) *p*-value				
	Total percent fat (%)	**Trunk fat mass (g)**	**Android fat mass (g)**	**Gynoid fat mass (g)**	**Android to gynoid ratio**
Total	0.19 (0.13, 0.24) <0.0001	291.60 (231.68, 351.53) <0.0001	73.86 (59.63, 88.08) <0.0001	55.69 (36.28, 75.10) <0.0001	0.01 (0.01, 0.01) <0.0001
Stratified by diabetes status					
Non-diabetes	1.32 (1.16, 1.49) <0.0001	1585.22 (1427.90, 1742.55) <0.0001	310.36 (276.47, 344.25) <0.0001	302.24 (254.49, 349.98) <0.0001	0.04 (0.03, 0.04) <0.0001
Prediabetes	0.45 (0.32, 0.58) <0.0001	780.17 (623.60, 936.74) <0.0001	152.58 (117.02, 188.15) <0.0001	100.92 (53.83, 148.01) <0.0001	0.01 (0.01, 0.02) <0.0001
Type 2 diabetes	−0.10 (−0.16, −0.05) 0.0001	−79.49 (−147.53, −11.46) 0.0221	−5.35 (−22.71, 12.01) 0.5461	−19.41 (−41.72, 2.90) 0.0884	0.00 (−0.00, 0.00) 0.5482

Age, sex, race, hypertension, hypercholesterolemia, smoking status, and vigorous work activity were adjusted.

TABLE 4 | Associations of glycohemoglobin (%) with adiposity.

	β (95% *CI*) *p*-value				
	Total percent fat (%)	**Trunk fat mass (g)**	**Android fat mass (g)**	**Gynoid fat mass (g)**	**Android to gynoid ratio**
Total	0.33 (0.19, 0.46) <0.0001	648.69 (511.22, 786.17) <0.0001	145.88 (112.54, 179.22) <0.0001	107.16 (61.65, 152.68) <0.0001	0.01 (0.01, 0.02) <0.0001
Stratified by diabetes status					
Non-diabetes	2.06 (1.69, 2.44) <0.0001	2831.87 (2472.91, 3190.84) <0.0001	535.24 (452.20, 618.27) <0.0001	607.61 (491.33, 723.88) <0.0001	0.04 (0.03, 0.05) <0.0001
Prediabetes	0.82 (0.49, 1.14) <0.0001	1992.63 (1604.47, 2380.79) <0.0001	400.58 (311.38, 489.78) <0.0001	199.11 (80.74, 317.48) 0.0010	0.04 (0.03, 0.05) <0.0001
Type 2 diabetes	−0.13 (−0.24, −0.01) 0.0403	−42.36 (−198.33, 113.60) 0.5945	4.36 (−35.69, 44.41) 0.8312	−34.61 (−86.21, 16.99) 0.1888	0.00 (−0.00, 0.01) 0.2261

Age, sex, race, hypertension, hypercholesterolemia, smoking status, and vigorous work activity were adjusted.

TABLE 5 | Associations of disease duration (years) with adiposity in patients with T2DM.

	β (95% *CI*) *p*-value				
	Total percent fat (%)	**Trunk fat mass (g)**	**Android fat mass (g)**	**Gynoid fat mass (g)**	**Android to gynoid ratio**
Total	−0.04 (−0.07, −0.01) 0.0143	−7.83 (−50.75, 35.09) 0.7208	−7.04 (−19.10, 5.02) 0.2529	−18.41 (−33.91, −2.91) 0.0201	−0.00 (−0.00, 0.00) 0.5460
Males	−0.03 (−0.08, 0.02) 0.2096	−0.90 (−62.59, 60.79) 0.9772	−2.67 (−19.77, 14.42) 0.7593	−8.14 (−28.03, 11.75) 0.4225	−0.00 (−0.00, 0.00) 0.4104
Females	−0.05 (−0.09, −0.00) 0.0370	−11.03 (−70.67, 48.61) 0.7171	−11.86 (−28.84, 5.13) 0.1717	−29.05 (−53.19, −4.92) 0.0186	0.00 (−0.00, 0.00) 0.9603

Age, sex, race, hypertension, hypercholesterolemia, smoking status, vigorous work activity were adjusted. Sex was not adjusted for in the subgroup analysis.

Therefore, the results of our study that trunk fat mass, android fat mass, gynoid fat mass, android to gynoid ratio as well as TPF were higher in patients with prediabetic and T2DM than those without DM could be explained. Lee's study found that the predicted fat mass and percent fat estimated by anthropometric prediction equations were also positively associated with the risk of T2DM (16). A study of Japanese Americans found that greater visceral adiposity preceded the development of T2DM and also demonstrated an effect independent of fasting insulin, insulin secretion, glycemia, total and regional adiposity, and family history of diabetes (17). Furthermore, the investigation of associations between adiposity phenotypes and risk for incident prediabetes and diabetes of 732 obese adults found that visceral adiposity, increased liver fat, decreased lower body fat, insulin resistance, elevated triglycerides, and low adiponectin levels were associated with incident prediabetes and diabetes in obese individuals (18). The pathologic process of this increased insulin resistance may include the following aspects: the accumulation of excess fat leading to the increase of plasma free fatty acid (FFA) levels in obese patients may interfere with muscle insulin sensitivity and the increased FFA of those intra-abdominal tissues drained by portal circulation may lead to high FFA in portal vein, which may inhibit the hepatic clearance of portal insulin in turn. Besides, obesity may also cause the increased cortisol and androgen secretion leading to lower insulin sensitivity in muscle tissue and liver and physical and chronic psychologic stress may play an important role in exacerbating insulin resistance, prediabetes, and T2DM (11, 19).

The present study also showed that TPF, trunk fat mass, android fat mass, and gynoid fat mass decreased as the disease duration of T2DM increased, although it was of no significance for trunk fat mass and android fat mass. This may be because once an individual was diagnosed with T2DM, the use of anti-diabetic drugs, the intervention of diet, and exercise may cause weight loss and decrease in fat mass, and the elimination of blood sugar through urination at an extremely high sugar level may also make some contributions (20). A large amount of evidence showed that diet and exercise interventions can manage obesity and impair glucose regulation in T2DM (21), and it showed that every 1 kg loss in weight reduced the risk of diabetes by 16% (22). The oxidation of FFA during exercise was associated with insulin sensitivity, metabolic flexibility, and body fat mass (23, 24). As for drug therapy for patients with T2DM, metformin still remains the first-line therapy choice, for its excellent role in reducing hepatic glucose output, enhancing insulin sensitivity and lowering HbA1c by about 1–2% (4). There were studies showing that metformin can decrease food intake and body weight (25), with weight loss preferentially involving adipose tissue (26). Glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide had been proved to sustain weight loss in obese patients and were associated with the reversal of prediabetes to normoglycemia during 1–2 years of follow-up (1) and another study showed that 3.0 mg of liraglutide was an adjunct to diet and exercise, associated with reduced body weight and improved metabolic control (27). In terms of insulin for the treatment of T2DM, a study by Haider showed that insulin or somatostatin infusion suppressed glucose-induced elevation of visfatin (a novel insulin-mimetic adipocytokine) (28), which can reduce fat accumulation and insulin resistance in patients with T2DM. All of these may coincide with the result of the decreased fat mass as the duration of T2DM increases in our study.

The blood glucose and HbA1c are considered as measures of DM control and parameters in relation to the risk of complications for decades. Of the two, HbA1c is more stable and convenient because of its absence of fasting (29). In this study, we found inverse associations of serum glucose and HbA1c with adiposity in patients with T2DM but direct correlations in those with prediabetes and without DM, which may be due to some drugs used for patients with T2DM being associated with weight gain in addition to their function of lowering blood glucose and HbA1c. In T2DM, there were 465 patients taking insulin and 1,436 patients taking glucose-lowering pills, with a few in prediabetes also doing so For example, sulfonylureas, such as gliclazide and glimepiride, were reported to have an association with hypoglycemia (30) and weight gain at the same time of their actions on β-cells to stimulate insulin secretion (31). Besides, thiazolidinediones, such as rosiglitazone and pioglitazone, were used clinically for improving of insulin sensitivity, might cause weight gain of up to 6 kg, which mainly because of fluid retention (4). Although insulin is an effective treatment to control blood glucose, weight and reduce HbA1c of 1.5–2% (4), it was also associated with a mean weight gain of 4 kg, especially in elderly patients (32). What's more, the bariatric surgery for those patients with T2DM and obesity was effective for weight reduction but also risky for hyperglycemia (33). Coincident with these findings, our study has implied that the simple measure of serum glucose, HbA1c or fat mass, and distribution may be insufficient to monitor the development and treatment effect of prediabetes and T2DM.

The main strengths of this study are the availability of a large, nationally representative population of US adults with data of fat mass and diabetes status from NHANES. Additionally, the availability of body composition measures by DXA offers additional information compared to the traditional measures of adiposity. More importantly, a large enough sample size allowed us to make the subgroup based on diabetes status and showed the distinct but neglected pattern of serum glucose and HbA1c with TPF and fat distribution that had never been reported in the previous studies.

This study also has several limitations. First, it is a cross-sectional study, which limits the inference of a causal correlation between serum glucose, HbA1c and TPF, fat distribution among adults. So, further basic mechanism research and large sample prospective study are still needed to identify the exact mechanism between them. Second, some NHANES participants were not eligible for a DXA scan because of excessive weight, height, or other reasons, so the estimates in this study might not fully represent the TPF and fat distribution in the general population. Third, there remains the possibility of bias caused by other potential confounding factors that we did not adjust for. Furthermore, some associations of disease duration, serum glucose, and HbA1c with adiposity in patients with T2DM were of no clinical or statistical significance, which may mainly because the number of patients with T2DM was small, so study

on a larger sample of patients with T2DM is eagerly needed. Besides, TPF defined by DXA may have several limitations, so the body fat mass and distribution in prediabetes and T2DM requires in-depth research in multiple areas such as diagnostic criteria for obesity in T2DM patients using TPF measured by DXA, alteration in fat mass since prediabetes or T2DM is diagnosed and its detailed mechanisms.

CONCLUSIONS

Our study indicated that adults with prediabetes and T2DM had significantly higher TPF, trunk fat mass, android fat mass, gynoid fat mass, and android to gynoid ratio compared with those without DM, and the fat mass decreased as the disease duration of T2DM increased. We also found inverse associations between serum glucose, HbA1c, and fat mass in patients with T2DM and direct association in those with prediabetes and without DM participants, which may give us a hint that just the measurements of serum glucose, HbA1c, or fat mass and distribution may be insufficient to monitor the development and treatment effect of T2DM.

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.

ETHICS STATEMENT

The Ethics Review Board of the National Center for Health Statistics approved all NHANES protocols.

AUTHOR CONTRIBUTIONS

JS and ZL contributed to data collection, statistical analysis, and writing and revising of the manuscript. ZZh and ZZe contributed to statistical analysis. WK supervised the study and contributed to polishing and reviewing of the manuscript. All authors contributed to the article and approved the submitted version.

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Individualized Nutritional Support for Hospitalized Patients With Oropharyngeal Dysphagia After Stroke: A Randomized Controlled Trial

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Objectives: Post-stroke dysphagia may cause aspiration pneumonia, malnutrition, dehydration, and other complications. However, data on the effects of nutritional supplementation and its value after stroke are insufficient. We aimed to evaluate the effect of an individualized 1-week nutrition intervention program on swallowing function and nutritional status in stroke patients with oropharyngeal dysphagia.

Methods: This study comprised the control group receiving oral nutritional support and continuous nasogastric tube feeding according to the results of the water swallow test (WST). The intervention group additionally underwent a volume-viscosity swallowing test (V-VST) and intermittent oroesophageal tube feeding based on WST. The outcomes were measured after 7 days of intervention, including the improvement of swallowing function assessment by WST, biochemical parameters, such as total serum protein, serum albumin, hemoglobin levels and body composition. This trial was registered with the Chinese Clinical Trial Registry, identifier ChiCTR 2100054054.

Results: In total, 173 participants completed the study between September 1, 2020, and April 30, 2021. Patients receiving individualized nutritional support showed a more significant improvement in the total effective rate of swallowing function (95.3% vs. 85.1%, $P < 0.05$). After the intervention, the total serum protein level (0.97 ± 0.41 vs. −0.83 ± 0.47 g/L; $P < 0.05$), serum albumin level (0.33 ± 0.28 vs. −1.39 ± 0.36 g/L; $P < 0.001$) and lean tissue mass (0.13 ± 0.35 vs. −1.00 ± 0.40 g/L; $P < 0.05$) increased in the intervention group. The decrease of hemoglobin levels in the control group was more evident (−6.17 ± 1.63 vs. −0.64 ± 1.40 g/L; 95%CI, −9.78 to −1.28; $P = 0.001$). The difference of phase angle between the two groups was statistically significant (5.93 ± 0.88° vs. 5.77 ± 0.78°; $P = 0.035$), but not in body fat mass.

Conclusions: In stroke patients with oropharyngeal dysphagia, the use of individualized nutritional support based on V-VST and intermittent oroesophageal tube feeding during the first week of hospitalization improved swallowing function and maintained nutritional status.

Clinical Trial Registration: https://clinicaltrials.gov/, identifier: ChiCTR 2100054054.

Keywords: stroke, oropharyngeal dysphagia, nutritional support, volume-viscosity swallow test, intermittent oroesophageal tube feeding

INTRODUCTION

Stroke has become the second leading cause of death worldwide (1). Oropharyngeal dysphagia (OD) is a common complication after stroke, with an incidence rate of OD within 3 days after stroke being 22–65% (2). The incidence rate of aspiration is >40% in patients with OD (3). OD can also cause a variety of other complications, including malnutrition, dehydration, and weight loss (4). In addition, the length of hospital stays and healthcare costs will increase with OD (5). Studies have shown that early detection of OD may reduce the risk of aspiration pneumonia and nutritional complications in stroke patients (6). However, the supporting evidence of nutritional support is insufficient, and there is growing interest about the effects of individualized nutritional support during the acute phase of stroke on swallowing function and nutritional status.

The diagnosis of OD requires clinical screening with the goal of quickly identifying patients at risk for OD who require clinical assessment. The 30-ml water swallowing test (WST) is a useful bedside screening tool for OD in stroke patients (7). In addition to clinical screening, the diagnosis of OD requires further clinical assessment. The volume-viscosity swallow test (V-VST) is a validated tool for the systematic assessment and clinical diagnosis of OD and provides accurate indications of the optimal bolus volume and viscosity for patients with OD. The diagnostic sensitivity and specificity of V-VST for OD can reach 93.17% and 81.39%, respectively (8). The design and implementation of texture-modified diet intervention based on V-VST results can effectively improve oral intake, weight, handgrip strength, and phase angle in older adults with OD (9).

Nutritional status may deteriorate during the first week after stroke, which is the first problem to be solved for stroke patients with OD. Studies have demonstrated that early nutritional support can improve the prognosis of patients at nutritional risk (10, 11). To facilitate recovery of swallowing function and improve the nutritional status of stroke patients, based on the two clinical screening and assessment tools mentioned above, we constructed an individualized nutritional management plan, provided graded nutrition management for stroke patients with OD according to the clinical assessment results, and made nurses play a leading role in the evaluation and intervention of swallowing disorders. The purpose of this study was to evaluate the effect of this individualized nutritional management plan on the swallowing function and nutritional status of stroke patients with OD, and hypothesize that it could improve the swallowing function of patients and maintain their nutritional status as much as possible.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Commitment of the First Hospital of Jilin University (registration number 20K056-001), in accordance with the ethical recommendations of the Declaration of Helsinki, and registered at the Chinese Clinical Trial Registry (ChiCTR 2100054054). All participants were fully informed and written consent was obtained.

Study Design and Participants

This study was a 7-day, single-center, randomized controlled, single-blinded, two-parallel group intervention study of post-stroke patients with OD. The study was conducted at the First Hospital of Jilin University, Changchun, China, between September 2020 and April 2021.

This study comprised consecutively admitted hospitalized stroke patients. According to the guidelines, all patients underwent formalized screening for OD by WST within 24 h after admission and before taking their first sip of water and food. Baseline evaluation was performed by registered nurses who were not co-investigators.

The inclusion criteria were as follows: (1) patients aged ≥ 18 years, (2) patients who met the diagnostic criteria of guidelines for the early management of patients with acute ischemic stroke (12) and underwent head computed tomography scanning or magnetic resonance imaging, (3) patients with Glasgow Coma Scale score ≥ 13 points, (4) patients with results of WST being II or above, and (5) patients with Nutrition Risk Screening 2002 score ≥ 3 points. The exclusion criteria were as follows: (1) patients with dysphagia before admission, (2) patients with significantly abnormal gastrointestinal function, frequent vomiting or diarrhea, or with enteral nutrition contraindications, (3) patients who had received enteral nutritional support before admission, (4) patients with poor compliance, who failed to complete follow-up, with incomplete clinical data, and with other conditions considered inappropriate for inclusion by researchers, and (5) patients and their immediate family members who did not want to be enrolled.

Patient characteristics were obtained through electronic medical records, which included the age, sex, comorbidity, National Institute of Health Stroke Scale (NIHSS) score, TOSTA criteria, length of stay, and hospitalization expenses.

Randomization

The patients were randomly divided into an intervention group ($n = 90$) and a control group ($n = 90$) at a ratio of 1:1 using a computer-generated random number table. Random assignment with treatment allocation information was sealed in non-transparent envelopes by a research assistant who was not involved in patient assessment and intervention. All participants and investigators were aware of group assignment, but the outcome assessment was performed by masked nurses and medical technicians.

Procedures

The multidisciplinary nutrition management team was composed of two neurology attending physicians, three neurology specialist nurses, a stroke health manager certified by the Stroke Prevention and Control Engineering Committee of the National Health Commission (13), a nutritional specialist and a rehabilitation therapist.

The attending physicians were responsible for clinical decisions and prescription of medical advice. Nurses were trained by rehabilitation therapists before performing the V-VST. The rehabilitation therapist was also responsible for swallowing therapy in both groups. The stroke health manager was responsible for providing advice to prevent malnutrition during hospitalization and to measure the human body composition of the two groups of patients. The dietitian worked with physicians and nurses to calculate adequate energy intake and guide the patient's diet.

Control Group

According to the results of the WST of patients in the control group, an appropriate way of eating was selected. Patients with WST level II were recommended oral nutritional support (ONS) with family managed nutrition. With WST level III and IV, the rehabilitation therapist comprehensively considered the patient's condition and swallowing ability and selected ONS or continuous nasogastric tube feeding. The preparation of family managed nutrition followed the principles of easy digestion, low-salt, low-fat, and high-quality protein diet and selected semiliquid or liquid food texture. Patients with WST level V patients had indwelling nasogastric tubes as per medical advice (**Figure 1**).

Enteral nutritional suspension (TPF) produced by Nutricia Corp., which is a non-elemental enteral nutritional agent, was selected for enteral nutrition preparation. The caloric value of TPF was 100 kcal/100 ml, and the energy prescription recommendation was 25–30 kcal/kg/day according to the 2016 Society of Critical Care Medicine and American Society for Parenteral and Enteral Guidelines for the provision and assessment of nutritional support therapy in critically ill adult patient (14).

Intervention Group

Patients with level II and III WST continued to use the V-VST for assessment (**Figure 2**). Different viscosities (nectar-like, pudding) were prepared using Resource Thicken Up (Nestle Company, Germany) and water. The volume of water was accurately measured using a syringe. The nectar-like viscosity was made up of 6.4 g Thicken Up and 140-ml water and the pudding viscosity was made up by adding 12.8 g Thicken Up to 140-ml water. Any signs of impaired safety (coughing, voice alterations, or a decrease in oxygen saturation of more than 3%) and impaired efficacy (labial seal, oral residue, pharyngeal residue, or repeated swallowing) were recorded during the assessment. The viscosity of the diet and liquid was determined according to the viscosity and volume tolerated in the V-VST.

For patients with level IV and V WST, intermittent oroesophageal (IOE) tube feeding and nasogastric tube feeding can be selected according to their personal preferences and tolerance. The enteral nutrition agents used in these two types of interventions were consistent with those in the control group. The caloric requirements were calculated by a dietitian using the Harris–Benedict estimation of basal energy expenditure. Daily protein intake was set at 1.2–1.5 g/kg. An individual nutritional plan was developed for each patient to reach these goals and caregivers of patients who underwent V-VST were taught to use thickeners to make diets with different viscosities according to the individual nutritional plan.

Outcome Measures

The primary outcome was the assessment of swallowing function by nurses using the WST. The specific efficacy criteria were as follows: Recovery were swallowing dysfunction disappeared and the outcome of WST recovered to level I. Effective, dysphagia symptoms improved, and WST improved by a grade. Significantly effective were swallowing disorders significantly improved and WST improved by two grades or more. The degree of dysphagia remained the same as before the intervention with no improvement in the WST (15). The total effective rates were calculated using the following equation:

$$Total\ efficacy\ rate = ([number\ of\ recovery + number\ of\ effective + number\ of\ significantly\ effective])/total\ number\ of\ patients \times 100\%$$

The secondary outcomes were biochemical parameters, including total serum protein, serum albumin and hemoglobin levels. Lean tissue mass, body fat mass and phase angle were measured by a stroke health manager using bioelectrical impedance analysis (BIA, Inbody S10, Biospace, Seoul, Korea). Measurements were performed before and after the intervention and in the supine position on an empty stomach in the morning. Phase angle was calculated using the following equation: Phase angle (°) = arctan (reactance/resistance) × (180/π). At the same time, we used unaffected side of limbs and trunk data for calculation to eliminate the effects of paralysis.

Sample Size Calculation

The sample size was calculated according to the data of An et al. (16), and the results showed that the total effective rate of improvement in swallowing function was 66.0% after standardized nutritional intervention compared with 28.0% in the control group. Therefore, the individualized nutritional support was able to improve the proportion of improvement in swallowing function by 38.0%. In fact, considering the short duration of intervention, we estimate that the actual

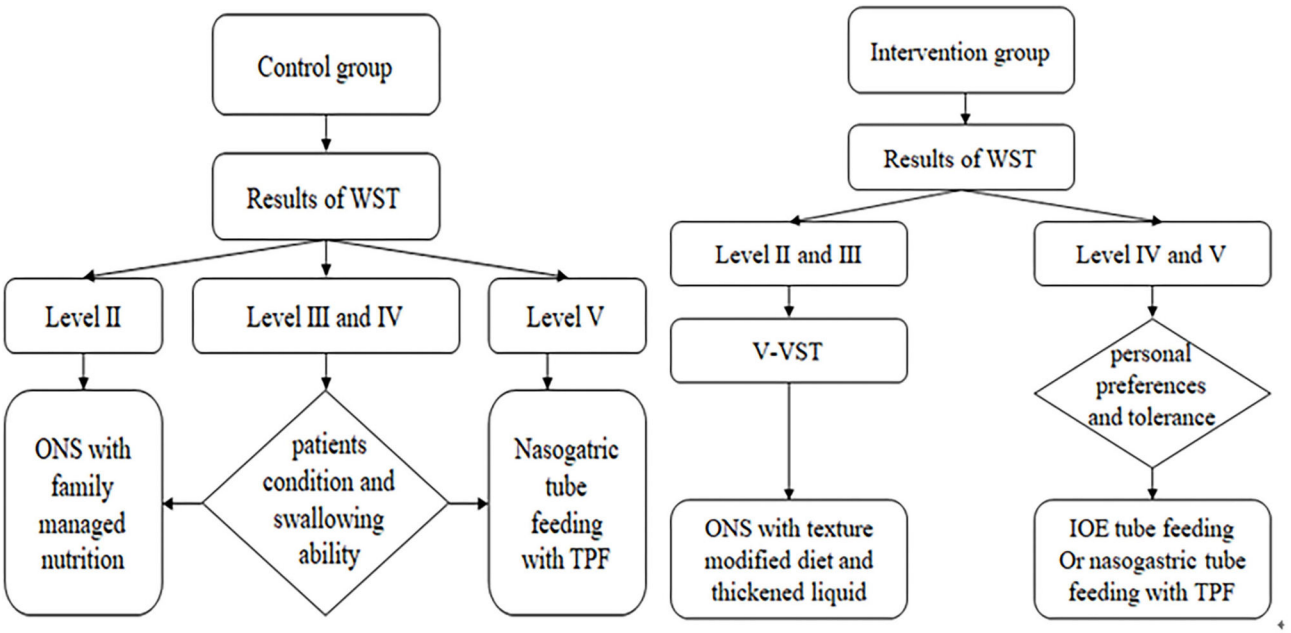

FIGURE 1 | Implementation basis and method of nutritional support. WST, water swallow test; ONS, oral nutritional support; TPF, enteral nutritional suspension; V-VST, volume-viscosity swallowing test; IOE, intermittent oroesophageal.

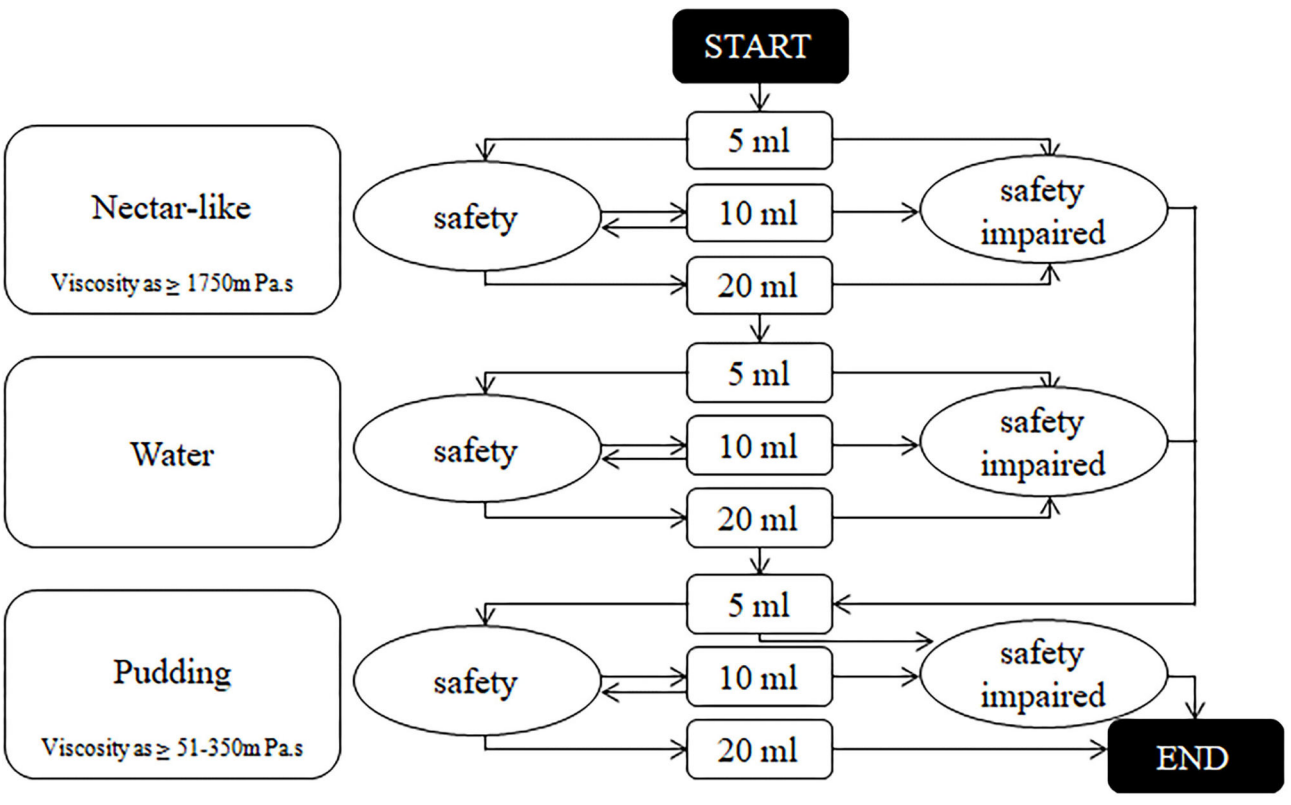

FIGURE 2 | The algorithm of volume-viscosity swallowing test. Output result was the viscosity and sip size of the previous stage before any signs of safety impaired.

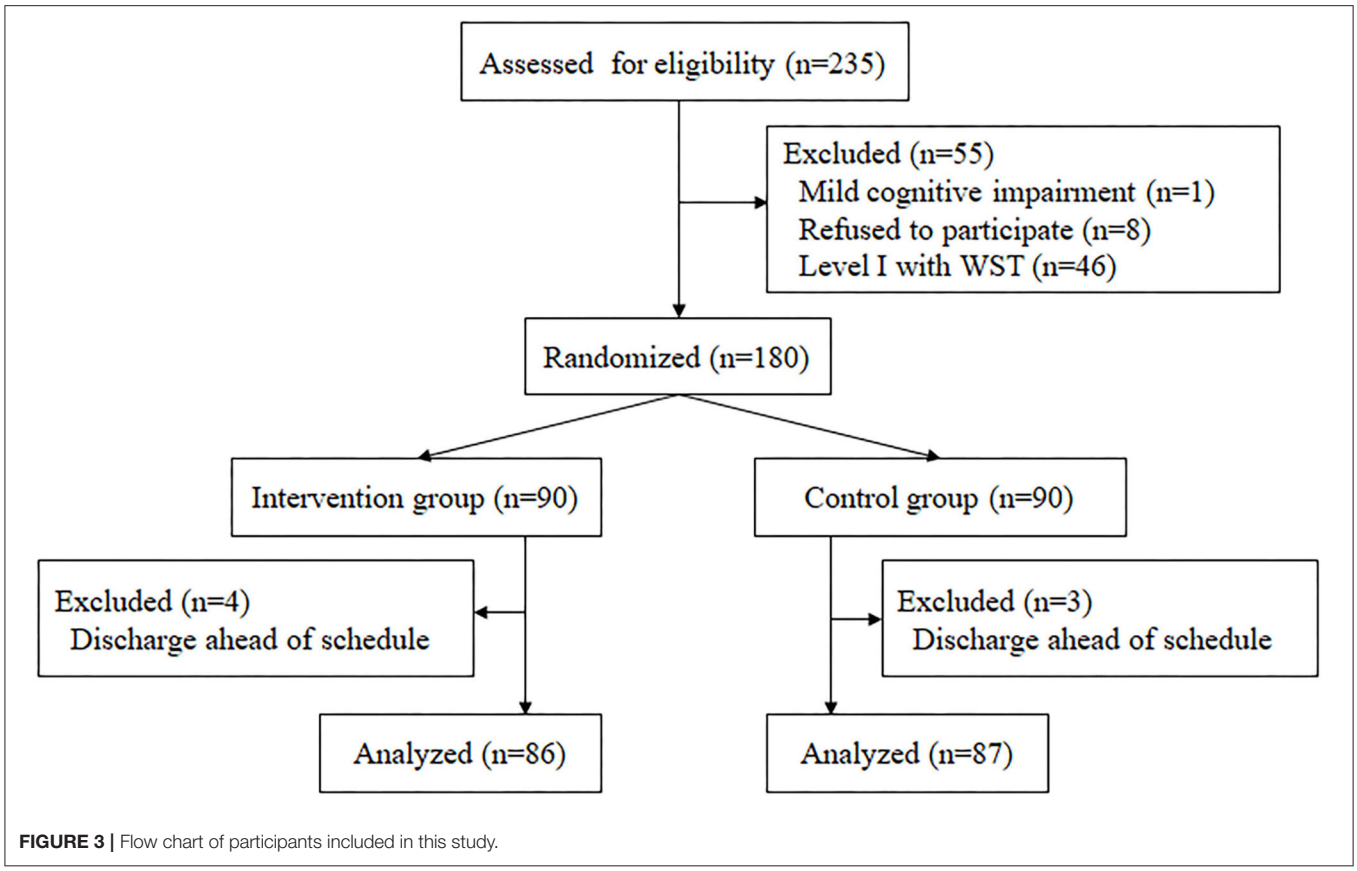

FIGURE 3 | Flow chart of participants included in this study.

TABLE 1 | Baseline characteristics between control and intervention groups.

Variables	Control group (n = 87)	Intervention group (n = 86)	t/χ^2	P value
Age (mean ± SD, years old)	61.79 ± 10.60	62.97 ± 10.60	−0.727	0.468
Gender (n, %)			1.113	0.292
Male	65 (74.7)	58 (67.4)		
Female	22 (25.3)	28 (32.6)		
TOSTA criteria (n, %)			1.230	0.894
Large artery atherosclerosis	36 (41.4)	33 (38.4)		
Cardioembolism	4 (4.6)	3 (3.5)		
Small-artery occlusion	2 (28.7)	31 (36.0)		
Other determined etiology	7 (8.1)	6 (7.0)		
Undetermined etiology	15 (17.2)	13 (15.1)		
Comorbidities (n, %)				
Stroke	29 (33.3)	18 (20.9)	3.362	0.067
Hypertension	57 (65.5)	48 (55.8)	1.707	0.191
Diabetes	32 (36.8)	21 (24.4)	3.111	0.078
Coronary heart disease/Atrial fibrillation	19 (21.8)	16 (18.6)	0.280	0.596
Dyslipidemia	21 (24.1)	29 (33.7)	1.933	0.164
Smoking	38 (43.7)	35 (40.7)	0.158	0.691
Alcohol use	34 (39.1)	27 (31.4)	1.119	0.290
NIHSS, median (IQR)	3.0 (1.0, 6.0)	3.5 (1.0, 8.0)	−0.473	0.636
Length of stay (mean ± SD, day)	9.72 ± 2.03	9.97 ± 2.29	−0.733	0.465
Hospitalization expenses (mean ± SD, yuan)	30,225.11 ± 20840.69	25,294.17 ± 19498.21	1.607	0.110

SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.

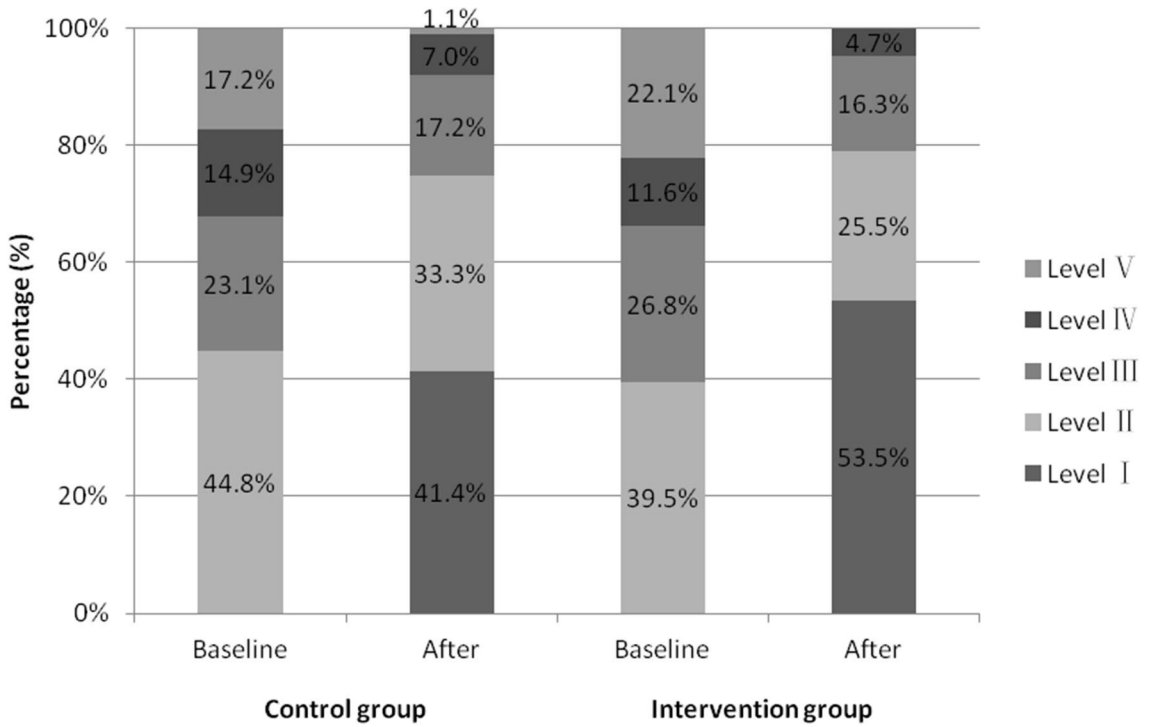

FIGURE 4 | Proportion of water swallow test results before and after seven days of intervention in two groups.

effect of individualized nutritional support may only reach 50% of the previous studies. In other words, we proposed that individualized nutritional support could increase the proportion of improvement in swallowing function by 19.0% at 7 days. Taking approximately 20% of dropout into account, a sample size of at least 90 participants per group was taken to reject the null hypothesis with a power of 0.9 and an alpha level of 0.05, which proves that the results of this study are effective.

Statistical Analyses

Descriptive analysis of the general data and the measurement data in accordance with the normal distribution are expressed as the mean ± standard deviation ($x \pm s$), and baseline comparisons between the two groups using independent sample *t*-tests and within-group changes were compared using paired *t*-tests. Measurement data that did not conform to a normal distribution were described by median and quartile range, together with the WST results, and the Mann-Whitney U test was used for comparison between the two groups. The counting data are expressed as a ratio of rate and composition and analyzed using the chi-squared tests or Fisher's exact test. Multiple linear regression model was used to examine the effectiveness of individualized nutritional support on nutritional status and body composition, adjusting for confounding factors like age, gender, comorbidities, and baseline value for each dependent variable. Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0. A two-tailed P value of < 0.05 indicated statistical significance.

RESULTS

Demographic Information

A total of 180 (90 in the intervention group and 90 in the control group) stroke patients with OD were included. During the study period, seven patients were excluded due to discharge ahead of schedule. Finally, 86 patients in the intervention group and 87 patients in the control group were analyzed (**Figure 3**). The baseline characteristics of the participants are presented in **Table 1**. There were no significant differences in age, sex ratio, medical history, smoking and drinking history, TOSTA criteria, and NIHSS scores between the two groups. The average length of stay and medical expenses did not differ significantly between the control and intervention groups.

Improvement of Swallowing Function

In the control group, 63 participants were received ONS with family managed nutrition, and 24 were fed via nasogastric tube. Fifty seven participants in the intervention group received ONS with texture modified diet, 10 received IOE tube feeding, and 19 received nasogastric tube feeding. As shown in **Figure 4**, there was no significant difference in the outcomes of WST at baseline between the intervention and the control groups ($Z = -1.455$, $P = 0.146$). One week after baseline, the total effective rate of the intervention group (95.3%) was higher than that of the control group (85.1%), the difference was statistically significant ($P < 0.05$; odds ratio, 0.278; 95% confidence interval [CI], 0.087–0.889; **Table 2**).

TABLE 2 | Improvement of swallowing function in the two groups.

	Recovery	Effective	Significantly effective	Total efficacy rate (%)
Control group ($n = 87$)	36 (41.4%)	24 (27.6%)	14 (16.1%)	74 (85.1)
Intervention group ($n = 86$)	46 (53.5%)	14 (16.3%)	22 (25.6%)	82 (95.4)
χ^2				5.169
P				0.023

TABLE 3 | Baseline values and changes in biochemical parameters and body composition after intervention in the two groups.

Variables		Control group ($n = 87$)	Intervention group ($n = 86$)	*t* / *F*	*P*
Total serum protein (g/L)	Baseline	66.21 ± 4.78	65.94 ± 5.24	0.348	0.729
	After	65.38 ± 4.82	66.91 ± 4.13	3.355	0.001[a]
	Δ	−0.83 ± 0.47	0.97 ± 0.41*	−2.907	0.004
Serum albumin (g/L)	Baseline	37.98 ± 2.50	37.96 ± 3.14	0.038	0.970
	After	36.59 ± 3.09	38.29 ± 2.58	5.000	<0.001[a]
	Δ	−1.39 ± 0.36*	0.33 ± 0.28	−3.806	<0.001
Hemoglobin (g/L)	Baseline	144.69 ± 12.97	143.22 ± 14.46	0.703	0.483
	After	138.52 ± 12.95	142.58 ± 12.04	2.747	0.007[a]
	Δ	−6.17 ± 1.63*	−0.64 ± 1.40	−2.569	0.001
Lean tissue mass (kg)	Baseline	23.96 ± 4.41	23.25 ± 4.22	1.088	0.278
	After	22.96 ± 3.18	23.38 ± 3.98	2.033	0.044[a]
	Δ	−1.00 ± 0.40*	0.13 ± 0.35	−2.143	0.034
Body fat mass (kg)	Baseline	21.82 ± 4.54	21.47 ± 5.86	0.439	0.661
	After	22.15 ± 4.82	21.68 ± 4.34	−0.613	0.541[a]
	Δ	0.34 ± 0.45	0.21 ± 0.44	0.200	0.842
Phase angle (°)	Baseline	5.96 ± 0.69	5.97 ± 0.90	−0.048	0.962
	After	5.77 ± 0.78	5.93 ± 0.88	2.130	0.035 [a]
	Δ	−0.19 ± 0.36*	−0.05 ± 0.46	−2.370	0.019

Change was presented as mean ± standard error of mean.
[a]*Adjusted for baseline value, age, gender, comorbidities and NIHSS.*
[Δ]*Change from baseline to seven days.*
[*]*Significant change within the group.*

Biochemical Parameters and Body Composition

The baseline biochemical parameters in the control and intervention groups were similar (**Table 3**). After the intervention, an increase in total serum protein level was observed in the intervention group, but not in the control group (0.97 ± 0.41 vs. −0.83 ± 0.47 g/L; 95%CI, −3.01 to −0.58; $P < 0.05$). Compared with the control group, serum albumin level was higher in the intervention group (36.59 ± 3.09 vs. 38.29 ± 2.58 g/L; $P < 0.001$). Hemoglobin levels in the two groups decreased, but the decrease in the control group was more evident (−6.17 ± 1.63 vs. −0.64 ± 1.40 g/L; 95%CI, −9.78 to −1.28; $P = 0.001$) than that in the intervention group.

Lean tissue mass remained largely unchanged in the intervention group compared to baseline, but slightly decreased in the control group(0.13 ± 0.35 vs. −1.00 ± 0.40 g/L; 95%CI, −2.17 to −0.09; $P < 0.05$), but there was no difference in body fat mass between the two groups. Individualized nutritional support kept the phase angle basically stable in the intervention group, while the control group decreased. After we controlled for age, gender, comorbidities, disease severity, and baseline values, the difference between the two groups was statistically significant (5.93 ± 0.88° vs. 5.77 ± 0.78°; $P = 0.035$).

DISCUSSION

In this study, we found that individualized nutritional support within the first week of hospitalization with modified texture diet, thickened liquids, and IOE tube feeding in this study improved swallowing function and effectively maintained the nutritional status of post-stroke OD patients. The higher overall effective rate of swallowing disorder improvement in the intervention group may be due to the implementation of IOE tube feeding. During oral intubation, the posterior pharyngeal and swallowing reflexes and promoted the recovery of swallowing function. Studies have shown that compared with continuous tube feeding, IOE tube feeding could significantly increase the rate of dysphagia function improvement by 5.22 times, increase total serum protein and serum albumin levels of stroke patients with dysphagia, and was more conducive to the conversion of patients to complete oral

feeding (17–19). According to the guidelines (20), we respect the wishes of patients and allow them to participate in treatment decision-making, which may help improve their cooperation and swallowing function. Sezgin et al.'s study also confirmed that fluid thickeners could improve swallowing functions (21).

Due to swallowing difficulties, patients with OD have reduced fluid and nutrient intake in both the acute and recovery stages of stroke (22). The European Society for Clinical Nutrition and Metabolism guidelines for neurology recommend screening for dysphagia in all patients with stroke before oral intake (23). As a tool for clinical screening of impaired swallowing safety and effectiveness in patients with dysphagia, V-VST can also direct healthcare personnel to better manage nutrition and reduce the risk of malnutrition (7). We performed V-VST for patients with WST at grade II and III in the intervention group, on the premise of ensuring safety and effectiveness as far as possible, selected the most appropriate food consistency and quantified the food volume for patients, reduced the chance of indwelling gastric tube for patients with swallowing disorders, and retained the normal eating experience of patients, which is conducive to the recovery of patients' diseases and improves their swallowing function, consistent with the results of Clavé et al. (24). The texture-modified diet and thickened liquids may increase the intake of patients in the intervention group. Therefore, compared with the family managed nutrition in the control group, the individualized nutrition management scheme better maintained the total serum protein, serum albumin and hemoglobin level.

The Academy of Nutrition and Diet and the American Society for Parenteral and Enteral Nutrition declared that loss of muscle is an important characteristic of malnutrition (25). After 7 days of intervention, the lean tissue mass of the control group decreased more, but the body fat mass between the two groups was not statistically significant, which may be due to the short intervention time. These two indicators will also be affected by the activity status after onset. The present study also used the Harris–Benedict equation to calculate the caloric requirement of patients, which was used by Otsuki et al. and improved the activities of daily living of older stroke patients in acute phase with malnutrition risk (26). The assessment of OD and individualized nutrition intervention in this study was performed mainly by nurses under the guidance and supervision of rehabilitation therapists and dietitians. Guo et al. also confirmed the role of nurses in a multidisciplinary team that improved the nutritional status of patients with dysphagia after stroke (27).

This study has some limitations. First, nutritional intervention was delivered for a relatively short period of time, and only the nutritional status and swallowing function of patients during hospitalization were observed. Second, the single-center and single-blinded design might have limited the general applicability of individualized nutritional support, which still needs to be examined. Third, the nutritional indicators used in this study may not objectively reflect the nutritional status of the patients. Follow-up investigations should be performed in future studies to observe the recovery of swallowing function and improvement of nutritional status and overall recovery after discharge. At the same time, whether the lean tissue mass and body fat mass can better reflect the nutritional status of stroke patients should be determined.

CONCLUSION

On the premise of safety and effectiveness, the individualized nutrition management scheme ensures the eating experience of patients to the greatest extent, increases the participation of patients in the process of disease treatment, respects the subjective feelings of patients, and effectively improves the swallowing function and nutritional status of stroke patients with OD.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commitment of The First Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Z-NG, YY, and X-LY conceived and oversaw the study. ZL, YS, X-YL, FM, JD, and Z-NG performed data collection and critically revised the manuscript. ZL and PZ performed statistical analysis. X-LY and ZL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Pathology and Physiology of Ileostomy

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An ileostomy is a surgery that is commonly performed to protect low pelvic anastomoses or prevent high-risk anastomotic leakages. However, various postoperative complications remain of major concern. After an ileostomy, the distal intestinal segment is left open for an extended period and is in a non-functional state. Consequently, the intestinal mucosa, smooth muscle, and microbiota undergo significant changes that are closely related to postoperative recovery and complications. A systematic description of these changes is necessary to understand the relationship among them and take more effective measures for postoperative intervention.

Keywords: mucosal barrier, microbiota, distal dysfunctional intestine, probiotics, ileostomy

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INTRODUCTION

An ileostomy is when the lumen of the ileum (small bowel) is brought through the abdominal wall *via* a hole that is created during an operation (**Figure 1A**). It is recommended as a remedial measure in many situations, including Crohn's disease and ulcerative colitis. It can protect and ameliorate an anastomotic leakage after a low pelvic anastomosis, or help to prevent a high-risk anastomotic leakage. With the advancement of medical technology, the anatomical position of anus-preserving surgery for low-lying rectal cancer is reducing, and there are increasing numbers of patients undergoing ileostomy. Whether in an elective setting or as an emergency, an ileostomy is considered a life-saving operative technique that maximizes the possibility of either helping save a patient's life or improving his or her quality of life (1). However, neither clinical research nor basic research has paid enough attention to the special physiological state of ileostomy in patients.

Patients who undergo ileostomy face a series of early or late complications. Ileostomies have the highest rate of complications compared to other ostomies, with the incidence of stomal complications ranging from 21 to 70% (2). In the early stages after an ileostomy, there is a high risk of fluid and electrolyte imbalance due to a high-output enterostomy. In the late stages, fistula-related enteritis, referred to as diversion colitis, may occur. Even after the reversal of ileostomy, the patient faces problems such as slow recovery and intestinal obstruction. These problems affect the quality of life of patients and need to be urgently addressed in the clinic. Therefore, it is necessary to dissect the pathology and physiology of ileostomy.

After an ileostomy, the distal intestinal segment is left open for an extended period in a non-functional state (**Figure 1B**). Before the reversal of ileostomy, the distal intestinal segment loses most of its receptivity to luminal stimulation, such as mechanical stimulation, and that from intestinal microbes and their metabolites. The environment of the intestines after an ileostomy is, to some extent, similar to that seen in patients with parenteral nutrition (PN), but enteral nutrition from the proximal intestine can nourish the distal intestine through the mesentery. Thus, the two conditions are different. As a result, the state of the fistula affects the function of the intestine and even the whole body, based on the morphology, composition, and function of the intestinal

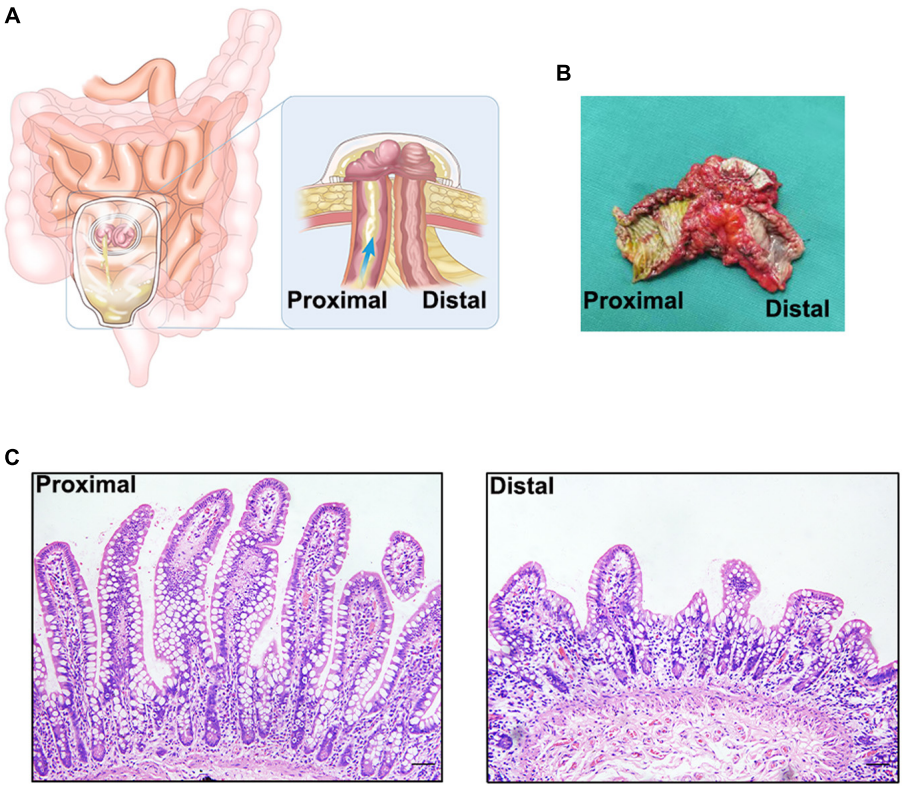

FIGURE 1 | (A). Schematic diagram of an ileostomy. **(B)** Ileal tissue from an ileostomy reversal, there is a significant difference between the proximal and distal intestinal tissue by visual inspection. **(C)** Hematoxylin-eosin staining of proximal and distal intestinal tissues. There is a significant atrophy in distal intestinal mucosa.

mucosa, smooth muscle, and microbiota. Previous studies have referred to the mucosal and muscle layer atrophy and microbial reduction in the distal dysfunctional segment, but there is a lack of systematic description of these changes and discussion of the possible clinical relationships. Thus, this review focuses on the changes in the distal dysfunctional segment, its comparison to intestinal changes in patients with PN, and the effect of luminal stimulation on the intestine and will provide some advice for certain clinical scenarios.

CHANGES IN MUCOSAL MORPHOLOGY

After an ileostomy, both the proximal and distal intestinal mucosa of the ileostomy show adaptive changes over time. Within a short period after an ileostomy, the mucosal thickness and villus height in the functional proximal segments of the intestines are significantly increased in both humans and mouse models (3–5). Mucosal hypertrophy and hyperplasia may compensate for the loss of function of the distal intestinal segment. However, after a long period after an ileostomy, these changes in the proximal intestinal mucosa may become less prominent in humans (5). Therefore, these mucosal changes may exert their effects during early adaptation, but not during late adaptation. In the distal dysfunctional intestinal segment of an ileostomy in humans, the intestinal mucosa undergoes atrophic changes in the absence of luminal stimulation (5, 6) (**Figure 1C**). Such atrophic changes may result from the decreased proliferation of the intestinal epithelium. RNA sequencing analysis of the distal intestinal mucosa after an ileostomy showed that the expression of genes related to proliferation, such as *Ki67*, is decreased. Wieck et al. found that although the expression of intestinal stem cell (ISC) markers, such as *LGR5*, and *ASCL2*, in the distal dysfunctional intestinal segment is increased, the number of ISCs is decreased (4). However, the preliminary results of our laboratory experiments showed that the ratio of ISCs to all epithelial cells in the distal dysfunctional intestinal segment is increased. The lack of luminal stimulation seems to minimize the impetus for ISCs to proliferate and differentiate but ISCs may have an enhanced stemness; such a state may be a physiological preparation for rapid recovery when luminal stimulation resumes. Although the cause of this special state remains unclear, a previous study confirmed that mechanical stimulation activates the Piezo1 protein to promote epithelial cell proliferation through the ERK pathway (7). Another study also demonstrated that mechanical stimulation promotes enteroendocrine cell differentiation through Piezo1 in the Drosophila model (8). Furthermore, single-stranded RNA is also sensed by Piezo1, which governs 5-HT production in enterochromaffin cells (9). Luminal stimulation including mechanical and microbial stimulation may be important signals for the proliferation and

differentiation of the intestinal epithelium to maintain integrity. However, this requires further exploration.

CHANGES IN TRANSPORTATION, DIGESTION, AND METABOLISM

In the human body, the small and large intestines have different functions. The small intestine is the key to the digestion and absorption of micro- and macro-nutrients. The large intestine is crucial for absorbing water, allowing proper defecation, and harboring intestinal microbes. Together, they form an important constituent of the body's digestive tract. However, ileostomy destroys intestinal continuity. As a result, the function of the intestines is altered significantly.

A key function of the large intestine is the absorption of water and salts; the ileostomy abolishes the entire function of the large intestine. In compensation, the function of the proximal intestinal segment increases. Clinical research has demonstrated that daily output after ileostomy (500–700 ml) is lower than the predictive value (1,000–1,500 ml) in most cases, and potassium excretion and sodium retention are significantly increased (10, 11). This may be due to changes in circulating aldosterone levels and mineralocorticoids. These hormones are elevated after ileostomy and are decreased again after loop ileostomy reversal (12, 13). In addition, in the ileal mucosa in a model of rat colectomy, the mRNA levels of epithelial sodium channel (ENaC) proteins were significantly increased compared with unoperated controls (14). Expression levels of ENaC proteins were also elevated in non-colectomized aldosterone-infused rats (15). An aldosterone-induced increase in sodium glucose co-transporter 1 (SGLT1) activity was noted in colectomized rats (15). The loss of function of the large intestine may lead to a decrease in the sodium absorption and a temporary decrease in blood sodium levels, which in turn leads to an increase in corticosteroids. Consequently, the sodium absorption function of the proximal intestinal segment is enhanced to adapt to an ileostomy and to avoid ileostomic diarrhea. In contrast, the capacity for transportation in the distal mucosae seems to be reduced. In patients who have undergone an ileostomy, both the expression of *SGLT-1* mRNA and glucose-coupled sodium transport were significantly reduced in the distal intestinal mucosa compared to the proximal intestinal mucosa (16). After performing loop ileostomies in rats, the *NHE-3* (coding Na (+)/H(+) exchanger) gene expression was attenuated in the distal dysfunctional ileal mucosa, and the *AQP3* (a water channel) mRNA levels were decreased in the distal dysfunctional region by 30–50% (17, 18). Luminal stimulation triggers intestinal mucosal transport, which is regulated by mineralocorticoids. Therefore, although the mineralocorticoid levels at the proximal and distal segments of the ileostomy are the same, the lack of luminal stimulation of the distal intestinal cavity reduces the transportation capacity of the distal segment.

In addition to transportation capacity, digestion and metabolism also change in the absence of luminal stimulation. In a clinical trial of patients with loop ileostomy, analysis of RNA sequencing showed that genes of the distal dysfunctional intestine that are associated with digestion, nutrient transport, and absorption were significantly upregulated, particularly those for fatty acids and cholesterol, which are over-represented pathways (4). Such changes may promote adaptation after ileostomy. The absorption area for vitamin B12 is limited to the ileum, and the reabsorption of bile acids takes place in the terminal ileum; an ileostomy may cause vitamin B12 and bile acid malabsorption (19), but this is yet to be confirmed. In addition, L-cells (one of the enteroendocrine cells) secrete peptide YY (PYY), which plays an important role in decreasing gastric emptying, pancreatic secretions, and small bowel motility; the net effect being the optimization of gut absorption (20). Previous studies have indicated that PYY secretion depends on the sensing of luminal nutrients, such as short-chain fatty acids (SCFAs) and bile acids (21, 22). Oh et al. found that mucosal PYY content in the distal dysfunctional mucosa was significantly lower than that in the proximal function ileum in the short term, but the two were similar in the long term (5). The reduction of PYY in the distal dysfunctional mucosa may result from loss of luminal stimulation, but this effect may be reversed by other body factors over a long period. Without luminal stimulation, the intestinal functional spectrum of digestion, metabolism, and transportation undergoes adaptive changes, but how the changes take place still requires further exploration. Some omics methods, such as plasma metabolomics and local proteomics, may be used to systematically study the effects of an ileostomy on the intestines and body.

CHANGES IN THE INTESTINAL MUCOSAL BARRIER

The gastrointestinal tract, which is exposed to countless microbes and environmental antigens, is the largest immune organ in the body. It forms a complex and complete mucosal barrier to prevent the invasion of foreign antigens. The mucosal barrier is mainly composed of chemical barrier, mechanical barrier, immune barrier, and biological barrier (23).

The chemical barrier is mainly composed of chemical substances secreted by the gastrointestinal tract such as mucin, gastric acid, bile, lysozyme, various digestive enzymes, and bacteriostatic substances produced by intestinal bacteria. The intestinal mucus barrier is an important part of the chemical barrier and is mainly controlled by goblet cells. Goblet cells are a group of specialized epithelial cells that synthesize secretory mucin glycoproteins (MUC2) and bioactive molecules such as epithelial membrane-bound mucins (MUC1, MUC3, and MUC17), Fc-gamma binding protein (FCGBP), trefoil factor peptides (TFF), and resistin-like molecule beta (RELMβ) (24). These active substances, along with water and inorganic salts, form a barrier on the surface of the intestinal mucosa, which plays an important role in preventing the invasion of foreign pathogens and intestinal microbes, maintaining the dynamic balance of intestinal mucosa, and regulating the microbial-host immune response. In patients who have undergone an ileostomy, the number of goblet cells in the distal intestinal mucosa is significantly reduced relative to the proximal intestinal mucosa

(25), and our studies also showed that the mucus layer of the distal intestinal mucosa is significantly thinner than that of the proximal intestinal mucosa (**Figure 2**). In mice with PN, although no changes were observed in total goblet cell numbers when compared with normal mice, levels of MUC2, RELMβ, and TFF3 in the ileum and luminal fluid were reduced (26). Similar to goblet cells, Paneth cells are specialized secretory epithelial cells resident in the small intestinal crypts of Lieberkühn (27). These cells secrete many dense granules such as lysozyme, secretory phospholipase A2 (sPLA2), α-defensins (cryptdins in mice), TNF, IgA, and RegIII, all of which balance the microbial population and mediate the inflammatory response to maintain intestinal homeostasis (27–29). These cells also secrete factors that help maintain and modulate the epithelial stem cells and progenitor cells that cohabitate in the crypts, which suggests that Paneth cells may play a major role in epithelial damage and repair (27). After an ileostomy, the Paneth cells in the distal intestinal mucosa of humans and mice are significantly decreased (3, 4) (**Figure 2**). In addition, following PN, there is reduced Paneth cell gene expression, such as sPLA2, and luminal levels of the proteins are also decreased (30). These results indicate that luminal stimulation may affect the proliferation, differentiation, and function of the goblet cells and Paneth cells, thereby affecting the chemical barrier.

The intestinal mucosal mechanical barrier generally consists of intestinal epithelial cells and tight junction proteins that connect them. As mentioned above, the distal dysfunctional intestine is atrophic; therefore, damage to the mechanical barrier is predictable. In addition, in a mouse model of colostomy, levels of occludin and E-cadherin were reduced in the distal dysfunctional intestinal segment, and the expression of claudin-3 was also decreased (31, 32). Regarding permeability, the absorption of fluorescein sodium and the permeability for mannitol and human serum albumin increased in the distal dysfunctional intestinal segment (33). These results indicate that the loss of luminal stimulation may lead to the reduction of tight junctions, which increases the permeability of the intestinal mucosa. Such destruction of the mechanical barrier is similar to that caused by PN; there are many reports on the destruction of the mechanical barrier caused by PN (34–36). As a result, some harmful substances, such as lipopolysaccharides (LPS), can easily enter the circulation through the intestinal barrier and cause abnormal reactions elsewhere in the body.

The immune barrier mainly consists of gut-associated lymphoid tissue (GALT), which consists of lymphocytes and lymphoid follicles in the intercellular space of the intestinal epithelium, lamina propria, and Peyer's patches (37). Under normal conditions, approximately 70% of the total active immune cells in the body participate in this compartment (38). GALT plays a significant role in the elimination of foreign pathogens through the intestinal mucosa, maintenance of intestinal immune tolerance, regulation of gut microbiota, and maintenance of intestinal homeostasis (37, 39, 40). In a study on patients who have undergone an ileostomy, compared with the proximal functional intestinal mucosa, a significant decrease in the number of CD3 lymphocytes spontaneously secreting IFN-γ was observed in the distal dysfunctional mucosa among both intestinal intraepithelial lymphocytes (p = 0.008) and Lamina propria lymphocytes (p = 0.007). Although less significant, similar results were obtained for IL-4, especially in lamina propria lymphocytes (41). Another study also showed ileostomy-induced immune modulation with a > 50% decrease in activated T cell numbers and an increase in that of regulatory T cells in patients with steroid-resistant acute graft-versus-host disease of the gastrointestinal tract (42). Consistent with this, a lack of luminal stimulation reduces the contact between the immune barrier and foreign antigens, which weakens the ability of the adaptive immunity. Similarly, PN results in a series of dramatic changes in the GALT compartment, such as decreased levels of Th2 cytokines, production and release of IgA on mucosal surfaces, and cellularity and function of lymphocytes in the Peyer's patch and lamina propria (43–45). Meanwhile, innate immune cells, such as neutrophils, accumulate and become primed, which may promote an inflammatory response (46). With these changes (**Figure 2**), the capacity for tolerance and adaptive response to previously encountered antigens of the intestinal barrier are reduced, leading to aggravated proinflammatory responses after injury, which seem to be associated with diversion colitis. Diversion colitis is a common non-specific inflammation of the malfunctioning bowel segment after diversion of feces, and intestinal immune disorders are an important risk factor (47). Loss of luminal stimulation seems to alter the immune balance of the distal dysfunctional mucosa and even of the rest of the body; this can temporarily relieve some intestinal immune diseases but may also cause intestinal inflammation in the long term. The biological barrier is not only affected by luminal stimulation, but is also part of the luminal stimulation which is discussed in the following sections in detail.

CHANGES IN INTESTINAL MICROBES

Gut microbes consist of approximately 10^{13} bacterial cells of more than 250 different species, as well as various fungi, viruses, and archaea, and comprise the largest symbiotic microbial community in humans (48). Due to long-term coevolution, such an abundant gut microbiota has become an integral part of the host and plays a significant role in nutrition absorption and metabolism, biological antagonism, activation and promotion of intestinal immunity, and maintenance of intestinal homeostasis, which have been described in detail previously (49–51). Due to the different local intestinal environments, the microbes in different parts of the intestines show different compositions and diversity, and most of the intestinal microbes are concentrated in the distal intestines. Toward the distal end of the digestive tract, the oxygen concentration in the intestinal cavity shows a downward trend, and the distal ileum and lower intestinal segments are basically in an anaerobic environment (52). Therefore, gut microbes are mainly anaerobic bacteria such as Firmicutes (60–80%), Bacteroidetes (20–40%), Proteobacteria, and Actinobacteria (53, 54). However, an ileostomy destroys the intestinal continuity and exposes the intestinal cavity to the external environment, which changes the intestinal microenvironment and affects the gut microbes.

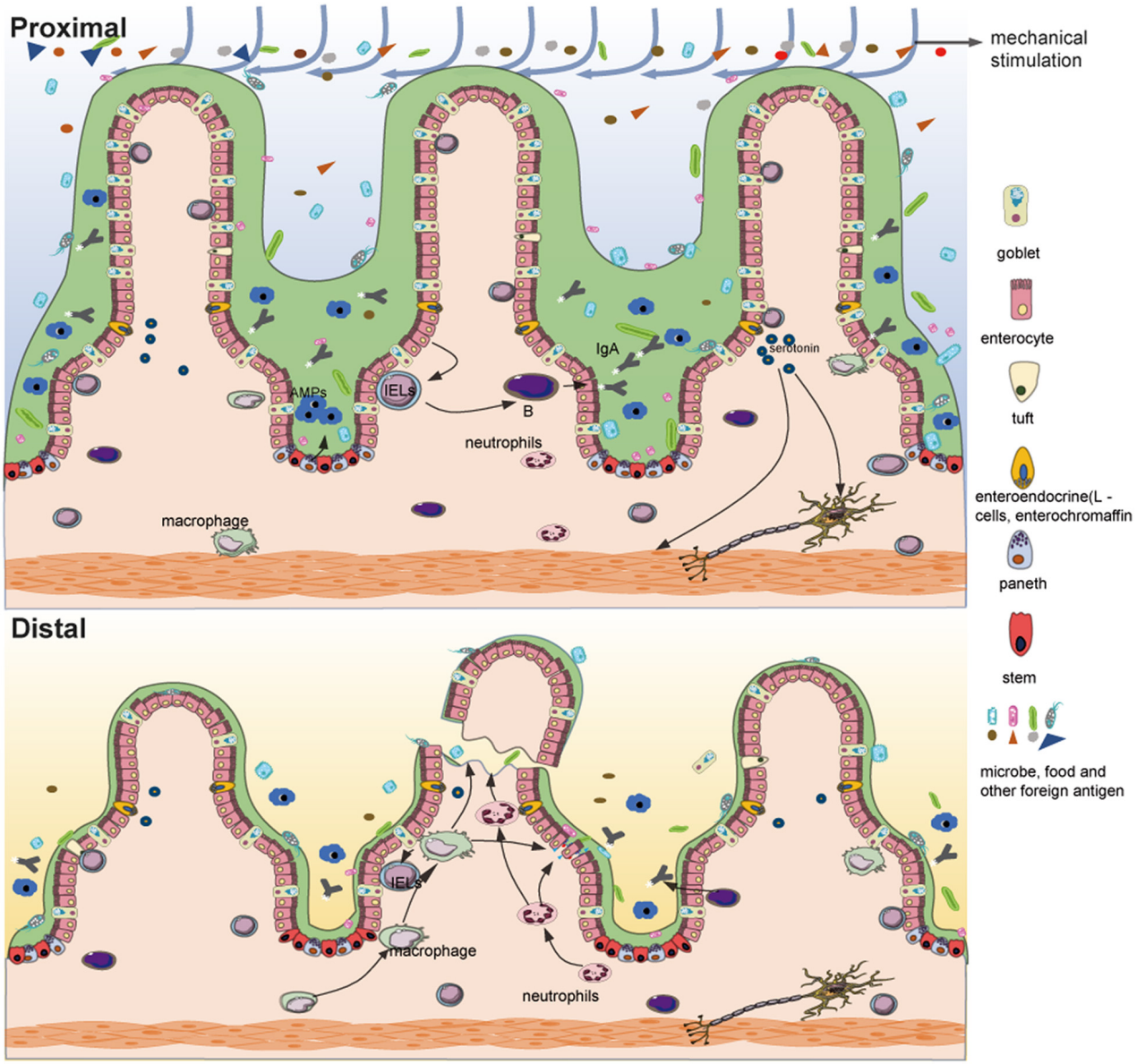

FIGURE 2 | Differences between the functional proximal intestinal segment and the non-functional distal intestinal segment of an ileostomy. Compared with the proximal intestinal segment, fragile and atrophic intestinal villi, a significantly reduced number of goblet cells, thinned mucus layer, decreased Paneth cells with fewer antimicrobial peptides (AMPs), reduced mucosal bacterial load and microbial diversity, decreased intestinal interepithelial lymphocytes, aggregated innate immune cells (such as neutrophils), atrophic muscular layer and possible reduction of serotonin are shown in the distal intestinal segment.

The survival of intestinal microbes depends on intestinal food contents and some endogenous secretions from the host, such as goblet cell mucin glycoproteins (55). Nevertheless, ileostomy dramatically changes the luminal environment of the distal ileum, which inevitably leads to microbial dysbiosis. *Via* a 16S rRNA gene analysis of the intestinal contents at both ends of ileostomy, Beamish et al. found that both the total mucosal bacterial load and microbial diversity were significantly reduced in the distal dysfunctional ileum compared with the proximal functional ileum (56). There was a significant reduction in the relative abundance of the Firmicutes phylum and a significant increase in that of the phyla γ-Proteobacteria and Bacteroidetes in the dysfunctional ileum when compared with the paired functional controls (56). The same changes were observed in the intestines of patients with PN (57), which is associated with intestinal inflammation (56). Furthermore, microbiome-metabolomic analysis of ileostomy indicated that the intestinal flora changed from strict anaerobes to facultative anaerobes before and after ileostomy, and returned to strict anaerobes after the reversal of ileostomy, suggesting that ileostomy permits oxygen entry in the lumen and promotes changes in intestinal microbial composition (58).

The reduction of bacterial load and microbial diversity may result in decreased competitive exclusion of pathogens, and an aerobic environment can stimulate the growth of certain pathogenic microbes. Previous studies have indicated that intestinal microbes are a factor leading to the occurrence and result of anastomotic leakages, and oral non-absorbable antibiotics can reduce but do not eliminate anastomotic leakage rates (59, 60). During the healing process of anastomotic tissues, some intestinal microbes, such as *Bacillus subtilis* strain (aerobic bacteria), *Enterococcus faecalis* (facultative anaerobes), and other facultative anaerobes produce a collagenase that can break down intestinal tissues at a rate seven orders higher than intestinal tissue collagenase. This is therefore likely to alter the dynamics of healing. These microbial-derived collagenases further trigger the production of matrix metalloproteinase 9 in intestinal tissues, which by itself possesses tissue-destruction capacities (61, 62). As a result, the process of healing that carries pathogenic bacteria becomes complex and can readily fail. In addition, microbial dysbiosis increases the risk of pathogen infection. After an ileostomy, a rare intestinal infection caused by methicillin-resistant staphylococcal enteritis has appeared clinically. Following PN, some opportunistic pathogens commonly related to infection, such as *E. coli*, *Salmonella*, *Vibrio*, and *Yersinia*, were observed (63). Compared with enteral feeding, experimental exposure of intestinal *C. albicans* during PN leads to increased colonization, mucosal translocation, and disseminated systemic infection (64). There is also a decrease in T cell numbers and IgA levels, as mentioned above. Fundamentally, the decline of intestinal mucosal immunity and the reduction of bacterial load and microbial diversity complement each other. As a result, pathogenic bacteria have a chance to grow, and abnormal immunity is activated.

In addition, the large intestine contains the largest bacterial ecosystem in the human body, constituting more than 70% of the symbiotic microbes in the body. The intestinal flora is usually discussed in the context of the disease state, which generally refers to the colonic flora (especially the flora derived from fecal metagenomic data) (65). The number of bacteria in the upper digestive tract is approximately 10^1–10^2 CFU/mL; in the ileum, about 10^4–10^8 CFU/mL; and in the distal colon, approximately 10^{10}–10^{12} CFU/mL (66). Many previous studies have shown that intestinal microbes and their metabolites are directly or indirectly related to the pathophysiology of various body systems (**Table 1**). From this perspective, ileostomy results in the loss of nearly 70% of symbiotic microbes, which means that ileostomy significantly affects all systems of the body. Intestinal microbes are closely related to various conditions, such as cardiovascular disease, obesity, and motor system diseases. Nevertheless, there are few reports on the abnormal outcomes of various systems after ileostomy. Clinical research on ileostomy has shown that patients have reduced bone mineral density and are more likely to have brittle fractures after surgery (67, 68). It has been confirmed that gut microbes play a central role in maintaining bone health and influencing bone turnover and density. Gut microbes indirectly regulate the absorption of calcium and the production of intestinal serotonin by regulating the immune system with SCFAs. Serotonin is a molecule that interacts with osteoblasts and is considered to be a bone quality regulator that regulates bone metabolism (69). Gut microbes are also involved in the bile acid metabolism, and the bile acid index of patients who have undergone an ileostomy appears to be abnormal based on our clinical observation. These results, however, indicate that gut microbes do not seem to be essential for survival. The body's strong compensatory ability may make up for the lack of intestinal microbes in a relatively short period. Further elucidation of the effects of the gut microbes on the body should provide more helpful insight on the postoperative recovery and prevention of further complications in patients.

CHANGES IN SMOOTH MUSCLE AND BOWEL MOTILITY

The intestinal smooth muscles mainly consist of longitudinal and circular smooth muscles, which generate coordinated motility

TABLE 1 | The microbial metabolites and compositions associated with human systems.

System	Microbial related substances	Disease (references)
Circulatory system	Lipopolysaccharides (LPS), trimethylamine (TMA), bile acids, short-chain fatty acids (SCFAs), phenylacetic acid, p-cresyl sulfate, indoxyl sulfate, anthocyanins, phytoestrogens	Cardiovascular disease (82)
Motor system	SCFAs, LPS medium chain fatty acids (MCFAs), tryptophan and tryptophan-derived metabolites, polyamines, TMA	Spondyloarthritis (83), Osteoporosis (84), Osteoarthritis (85)
Endocrine system	SCFAs, γ-aminobutyric acid (GABA), circulating branched-chain amino acids (BCAAs), serotonin (5-HT), other neurotransmitters (NTs), LPS, trimethylamine N-oxide (TMAO), tryptophan-derived indoles, bile acids	Obesity (86), Type 2 diabetes mellitus (87)
Nervous system	SCFAs, GABA, 5-HT, other NTs, amyloids, LPS, histamine, dopamine, endotoxin, hydrogen, hydrogen sulfide (H_2S), indoleacetic acid	Alzheimer's Disease (88), Parkinson's disease (89)
Digestive system	LPS, SCFAs, urolithins, bile acids, tryptophan, succinate, ethanol, H_2S, polyamines, toxins	Cancer (90), Inflammatory bowel disease (91)
Urinary system	Tryptophan, SCFAs, LPS, TMAO, Phenols, indole	Kidney disease (92, 93)
Respiratory system	LPS, SCFAs, microbe-associated molecular patterns	Chronic Obstructive, Pulmonary Disease, Asthma, Cystic Fibrosis (94, 95)

patterns to promote full digestion, absorption, and emptying of intestinal contents. Such coordinated motility of the intestine is not only under multiple levels of control, including the enteric nervous system (ENS), central nervous system (CNS), intestinal hormones, and paracrine agents, but is also related to other factors such as gut microbes and mechanical stimulation of intestinal contents (70, 71). Consideration of ileostomy may provide some insight.

After an ileostomy, the intestinal motility of the distal dysfunctional intestinal segment is markedly decreased, which may be an important cause of postoperative ileus following the reversal of ileostomy (72, 73). The postoperative ileus is the most common complication after the reversal of ileostomy; the reported incidence is usually between 15 and 32% (74). What leads to a loss of intestinal motility? From the perspective of effectors, similar to the atrophy of the intestinal mucosa, the strength and area of intestinal smooth muscle are both significantly reduced (6) (**Figure 2**). Disuse atrophy may result from the loss of mechanical stimulation of the intestinal contents. From the perspective of the controller, in the bypass ileum of the rat model, the number of neurons expressing pituitary adenylate cyclase-activating peptide, neuropeptide Y, or vasoactive intestinal peptide decreased gradually, and the number of neurons expressing nitric oxide synthase increased significantly, especially in the intermuscular ganglion (75). In rabbits with a colostomy, the nitrergic-peptidergic, cholinergic-peptidergic, and non-cholinergic–non-nitrergic responses in the distal colonic segment were significantly decreased compared with those in the control group (76). Neural activities related to contraction and relaxation seem to be reduced, but the relaxation responses are relatively stronger, which may contribute to the hypomotility noted in inactive intestines. From the perspective of regulators, gut microbes influence intestinal motility in a variety of ways; for instance, gut microbes indirectly affect intestinal motility by producing metabolites, such as SCFAs, and peptides to stimulate the ENS, or by influencing the production of serotonin (**Figure 2**), and they can also directly affect intestinal motility through Toll-like receptors (the bacterial recognition receptors) expressed by smooth muscle cells (70, 71, 77). The relationship between intestinal motility and gut microbes has previously been elaborated, but there are still many questions left to answer (78). In addition, bile acid and mucus also participate in the regulation of intestinal motility, which suggests that the loss of bile acid and mucus may be an important cause of the hypomotility noted in the distal dysfunctional intestinal segment (78). Disturbance of intestinal homeostasis also leads to abnormal motility of the intestines.

Based on the factors mentioned above, a new method for stimulation of the distal dysfunctional intestinal segment with probiotics and prebiotics before the reversal of ileostomy has been attempted in clinical practice (79–81). The results showed that it promotes the recovery of postoperative intestinal function and reduces the incidence of ileus; however, there is insufficient high-quality evidence to recommend routine implementation of preoperative bowel stimulation in clinical practice. Questions on the target and period of stimulation still require further research.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

An ileostomy is an operation with both benefits and risks, and effective promotion of postoperative recovery and prevention of complications have been unsolved clinical problems for a long time. Understanding the physiological and pathological changes in patients who have undergone an ileostomy will help solve these. Previous studies have shown that intestinal stimulations, such as mechanical stimulation and that from intestinal microbes, have various effects on the intestinal mucosa. Based on this, some medical measures, such as postoperative enema with probiotics or normal saline, have been tried in the clinic, but their effects have not been satisfactory. The postoperative state of patients who have undergone an ileostomy is complex and requires a standardized evaluation system. More evidence-based medicine studies are needed to establish effective and standardized postoperative interventions for ileostomy.

In addition to focusing on the clinical issues that are related to an ileostomy, the conditions of an ileostomy can be ideal to study various experimental questions. As the colon is left unused for a long time, the metabolism of some drugs or foods in the small intestine can be studied by testing the stool of the small intestine. Generally, the ileostomy is reversed after half a year, and the distal intestinal microbes undergo a process from loss to reconstruction during this period. Microbiomics can be used to understand how the microbes at the distal intestinal segment are naturally rebuilt; this will further contribute to the study of the dynamic evolution of gut microbes. Additionally, based on the influence of gut microbes on body metabolism, studying this process using metabolomics linked to microbiomics can further elucidate the relationship between metabolism and gut microbes. This will, in turn, provide more valuable suggestions for postoperative recovery and prevention of complications after ileostomy. Of course, such questions can also extend to colostomy and the relationship between ileostomy and cancer and inflammatory bowel disease. Answers to some of these questions may not only explain some normal physiological changes but also help solve clinical problems related to fistulas.

AUTHOR CONTRIBUTIONS

HM conceived and wrote the manuscript. YQ and WX contributed to the writing and revision of the manuscript. XL and HY participated in the discussion of issues related to ileostomy. All authors contributed to the article and approved the submitted version.

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Body Composition Characteristics of Community-Dwelling Older Adults With Dynapenia

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This study aimed to determine the differences in muscle and fat masses of the arm and leg between older adults with dynapenia, sarcopenia, or presarcopenia and normal individuals. The percent body fat, lean body mass, and skeletal mass index were measured with bioelectrical impedance analysis. Muscle function was evaluated using grip strength and walking speed. Participants were classified into four categories. Dynapenia was defined as low muscle function with normal muscle mass. Sarcopenia was defined as the presence of both low muscle mass and low muscle function. Presarcopenia was defined as low muscle mass with normal muscle function. Control was defined as normal muscle mass and function. Multivariate analyses of variance were performed separately for women and men to test the main effect of sarcopenia category on body composition. Among the 356 enrolled participants, 270 were women, and 86 were men. In older women, the dynapenia and sarcopenia groups had significantly less muscle mass in the leg than the control group. In older men, the dynapenia group demonstrated a higher body fat mass in the leg than the control group. These results suggest that different strategies are necessary to prevent dynapenia in women and men.

Keywords: bioelectrical impedance analysis (BIA), body fat, leg, muscle function, muscle mass

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INTRODUCTION

Dynapenia is defined as an age-related loss in muscle strength in older adults that negatively affects their medical conditions, including metabolic syndrome (1), dementia (2), or mortality (3). Additionally, dynapenia is associated with abdominal obesity that worsens older adults' ability to perform instrumental activities of daily living over time (4). Although dynapenia is prevalent in older adults with reduced skeletal muscle mass, a specific population exhibits the loss of muscle strength despite having normal skeletal muscle mass (5). Based on the classification of sarcopenia suggested by the European Working Group on Sarcopenia in Older People (6), recent studies have defined dynapenia as the loss of muscle strength with normal muscle mass (7–11) to differentiate this condition from sarcopenia when describing the age-related loss of muscle mass and function. In a previous study, dynapenia prevalence rate was 10% among 213 Japanese older adults aged ≥60 years (12), whereas sarcopenia prevalence rate was 5.5–25.7% in previous studies involving Japanese older adults (13).

Dynapenia, which is mediated by physiological neuromuscular adaptations, is influenced by increases in body fat with consequent infiltration of intramuscular fat; thus, the loss of muscle function is not merely a result of sarcopenia (14–18). A previous study evaluating skeletal muscle characteristics in dynapenia, sarcopenia, and presarcopenia demonstrated that skeletal muscle

characteristics of dynapenia vary markedly from those of presarcopenia, which is defined as having low skeletal muscle index but normal muscle function (11). The abovementioned study also indicated that older adults diagnosed with dynapenia or sarcopenia have a lower knee extension torque than both normal older adults and those with presarcopenia (but not those with both dynapenia and sarcopenia) (11). Additionally, a cross-sectional study showed that older adults with dynapenia had decreased thicknesses of the rectus femoris and medial gastrocnemius muscles compared with those without dynapenia (7). Another study reported that older adults with dynapenia have a higher body mass index and fat mass than adults with sarcopenia and presarcopenia (8). The extremities may also have varying muscle and fat masses in dynapenia, sarcopenia, and presarcopenia compared with normal older adults. Moreover, it may be different in men and women, as men have a higher ratio of muscle to fat than women (19). However, appendicular muscle and fat masses of older adults with dynapenia, sarcopenia, or presarcopenia have not been compared with those of normal older adults.

Therefore, this study aimed to evaluate the difference in appendicular muscle and fat masses of the arm and leg between older adults with dynapenia, sarcopenia, or presarcopenia and normal older adults. We hypothesized that skeletal muscle and fat masses of limbs would vary significantly between older adults with dynapenia, sarcopenia, or presarcopenia and those without dynapenia or sarcopenia.

METHODS

Study Design

The study design was cross-sectional. Data on socio-demographic information (age, gender), body composition, and physical function were collected. All parameters were essential for assessing the participants' functional status and were not harmful. All procedures were conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects of 1975. This research has been approved by the institutional review board of the author's affiliated institution (IRB number 02-05).

Setting

The participants were recruited through the staff of community centers, regional comprehensive support centers, and gymnasiums in the Hiroshima Prefecture in Japan. A flyer with an outline of the survey was also used for recruitment. Recruitment and data collection were performed between November 2020 and December 2020.

Participants

Participants included in the study were (1) community-dwelling persons aged 65 years or older, and (2) persons with independent mobility [Barthel Index mobility score $>$ 10 (full score 20)] (20). The exclusion criteria were as follows: (1) suspected cognitive impairment [mini-mental state test $<$ 23 (full score 30)] (21) and (2) serious illness (unstable cardiovascular disease, stroke, severe respiratory impairment, Parkinson's disease, diabetic peripheral neuropathy, or rheumatoid/arthritis). All participants provided written informed consent. People with suspected cognitive impairment were excluded to ensure the accuracy of the responses to the questionnaire survey. People with suspected serious diseases were excluded to prevent falls during measurement and to avoid worsening of diseases.

Body Composition

Lean body mass (LBM) and body fat mass (BFM) were measured using the bioelectrical impedance analysis (BIA) method. The BIA was performed for both arms and legs. InBody 270 (InBody Japan Inc., Tokyo, Japan) was used to measure the LBM, BFM, and appendicular skeletal mass index (ASMI)—calculated as the skeletal muscle mass of the extremities—and then normalized by height squared (m^2) (22). InBody 270 is an acceptable device for body composition analysis (23). Participants' hands and feet were wiped down with InBody tissues to increase their conductivity. Participants' feet were aligned with the foot electrodes. Their thumbs were placed on the oval electrodes. Participants needed to keep their arms straight and hold the handles away from their bodies at a 45° angle. They had to stay still and maintain the testing posture until the test was completed. The weight measured was subtracted by 0.8 kg, considering the garment weight. The examiner in charge of measuring body composition received training to use InBody 270, and thus, the examiner was familiar with the technique. Measurements were not necessarily performed in the fasting state.

In this study, the LBM and BFM represented the indices of muscle mass. Each site-specific LBM (kg) was divided by the height squared (m^2) and used as the value for each region (kg/m^2) in subsequent statistical analyses. The mean values of the left and right sides were used for analysis.

Sarcopenia Category

Muscle mass and function were used as indicators to classify the participants into four groups (**Figure 1**). ASMI represented the index of muscle mass. Grip strength (muscle strength) and walking speed (physical performance) were used to determine the presence of low muscle function. Sarcopenia categories were classified into four groups: dynapenia, sarcopenia, presarcopenia, and control. We defined dynapenia as low muscle function with normal muscle mass (11). Low muscle function was defined as having weak handgrip strength and/or slow walking speed (13). Sarcopenia was operationally defined using the diagnostic algorithm of the Asian Working Group for Sarcopenia (AWGS) based on the presence of both low muscle mass and function (13). Presarcopenia was defined as low muscle mass with normal muscle function (14). Control was defined as having normal muscle mass and function.

For the measurement of walking speed as a physical performance, the test participant walked along a 5-meter walking path according to the instructions (24). A spare path of 1 m was provided in front of the walking path. The teaching was unified with "Walk forward as if you were always walking." Measurements were taken to the first decimal place and rounded to the second decimal place. Walking speed was measured only once.

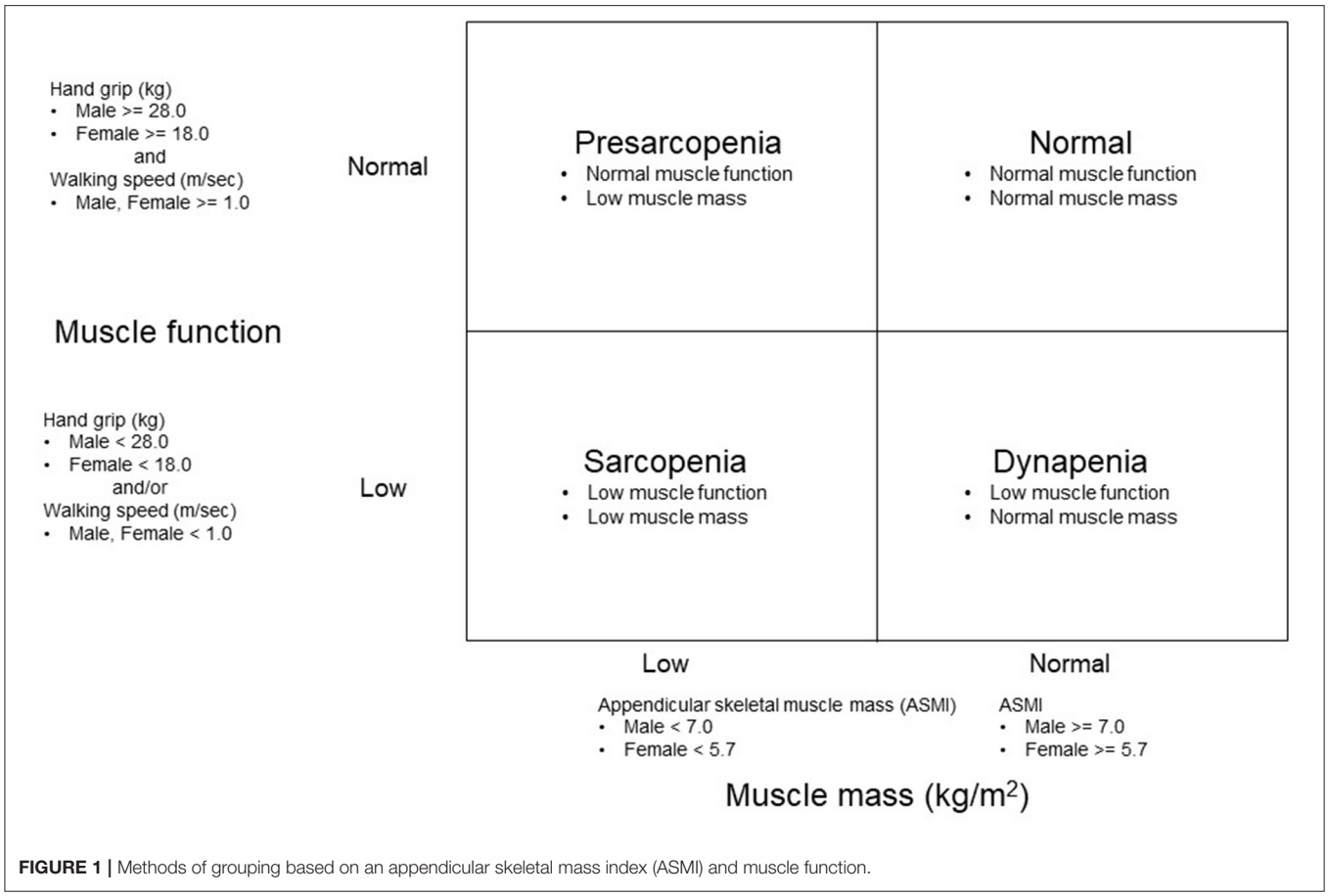

FIGURE 1 | Methods of grouping based on an appendicular skeletal mass index (ASMI) and muscle function.

For the measurement of grip strength as an indicator of muscle strength, we used a grip strength meter (TKK 5401 Grip-D; Takei, Niigata, Japan) (25). The test participant grasped the grip strength meter so that the pointer of the meter was on the outside. Before the measurement, the interphalangeal joints of the fingers were adjusted so that they were almost at right angles.

Measurements were taken once on both sides. Records were made in kilograms, and those less than a kilogram were rounded down. The record of the better left or right side was used for subsequent analysis.

Statistical Analysis and Sample Size

The multivariate analysis of variance (MANOVA) was performed to evaluate the main effect of sarcopenia category on body composition (LBM of arm, LBM of leg, BFM of arm, and BFM of leg). We did not use the analysis of variance (ANOVA) test because multiple ANOVAs increase type 1 error. MANOVAs were performed separately for women and men. The main effects of the sarcopenia category on LBM and BFM, respectively, were examined after confirming a significant main effect of the sarcopenia category in the MANOVA. For body composition, for which the main effect was significant, multiple comparisons were performed using the Dunnett's method to compare the values of the control and dynapenia, sarcopenia, or presarcopenia groups. The significance level was set at 5%. JMP® Pro ver. 16.0.0 (SAS Institute Inc., Cary NC, USA) was used for all statistical analyses.

The sample size required to ensure sufficient power in the MANOVA was calculated. G*power 3.1.9.7 was used for this calculation (26). The parameters were set as follows: effect size = 0.15, significance level = 0.05, effect size = 0.80, number of groups = 4, and response variables = 4. The result of the calculation demonstrated that a sample of 44 people (11 people in each group) was required to correctly detect a significant difference among the groups.

RESULTS

The study included 356 participants (270 women and 86 men). The socio-demographic information of the participants is shown in **Table 1**. No missing data were handled. The numbers and percentages of people in each sarcopenia category were as follows: 65 participants in the sarcopenia group (47 women, 17.4%, 18 men, 20.9%), 96 participants in the presarcopenia group (78 women 28.9%, 18 men 20.9%), 52 participants in the dynapenia group (36 women 13.3%, 16 men 18.6%), and 143 participants in the control group (109 women 40.4%, 34 men 39.6%).

The body composition for each sarcopenia category is shown in **Table 2.** In women, the results of the MANOVA showed that

TABLE 1 | Background information.

(A) Women

		Control	Dynapenia	Sarcopenia	Presarcopenia	*F*-value
Number		109	36	47	78	
		40.4%	13.3%	17.4%	28.9%	
Age	(ys)	72.0	77.0**	77.9**	74.0*	16.753
	4.4	6.8	6.3	5.3		
Walking speed		1.34	1.00**	1.01**	1.36**	44.915
	(m/sec)	0.21	0.28	0.28	0.20	
Grip strength		23.4	17.6**	17.3**	21.4**	58.729
	(kg)	3.3	4.7	2.8	2.0	
BMI	(kg/m^2)	23.8	24.8	21.0**	21.0**	27.172
		2.9	3.8	2.7	2.4	
LBM	(kg)	35.8	34.9	30.5*	31.1*	83.249
(whole body)		3.0	2.6	1.9	1.7	
LBM	(kg)	1.7	1.7	1.4*	1.4*	61.535
(right arm)		0.3	0.2	0.2	0.2	
LBM	(kg)	1.7	1.7	1.4*	1.4*	54.649
(left arm)		0.3	0.2	0.2	0.2	
LBM	(kg)	16.2	15.9	13.7*	14.1*	58.535
(trunk)		1.6	1.4	1.1	1.0	
LBM	(kg)	5.7	5.2*	4.4*	4.8*	83.261
(right leg)		0.6	0.6	0.5	0.5	
LBM	(kg)	5.7	5.2*	4.4*	4.7*	81.451
(left leg)		0.6	0.7	0.5	0.4	
ASMI	(kg/m^2)	6.17	6.07	5.18**	5.30**	135.017
		0.43	0.37	0.34	0.25	
BFM	(kg)	19.2	19.6	14.3*	15.4*	14.079
(whole body)		5.6	6.9	5.6	4.5	
BFM	(kg)	1.3	1.4	1.0*	1.1*	9.913
(right arm)		0.5	0.7	0.5	0.3	
BFM	(kg)	1.4	1.4	1.0*	1.1*	10.106
(left arm)		0.5	0.7	0.5	0.4	
BFM	(kg)	9.2	9.6	6.7*	7.3*	13.768
(trunk)		3.0	3.5	3.1	2.5	
BFM	(kg)	3.1	3.1	2.3*	2.5*	15.315
(right leg)		0.8	1.0	0.8	0.7	
BFM	(kg)	3.1	3.0	2.3*	2.5*	15.111
(left leg)		0.8	1.0	0.8	0.7	
Total body	(kg)	27.9	27.3	23.9*	24.3*	83.072
water		2.3	2.0	1.5	1.3	

(B) Men

		Control	Dynapenia	Sarcopenia	Presarcopenia	*F*-value
Number		34	16	18	18	
		39.6%	18.6%	20.9%	20.9%	
Age	(ys)	73.8	75.6	81.9**	78.3*	9.664
	4.1	5.7	5.5	6.9		
Walking speed		1.28	0.88*	1.08*	1.19*	16.602
	(m/sec)	0.16	0.14	0.29	0.18	
Grip strength		36.1	35.0	24.7**	31.6**	21.513
	(kg)	4.1	7.4	5.6	3.2	

(Continued)

TABLE 1 | Continued

(B) Men

		Control	Dynapenia	Sarcopenia	Presarcopenia	*F*-value
BMI	(kg/m^2)	23.7	25.3	22.1*	21.2**	11.635
		2.4	2.2	2.1	2.1	
LBM	(kg)	47.3	45.1	37.6*	40.7*	31.258
(whole body)		4.2	3.7	3.8	2.6	
LBM	(kg)	2.7	2.6	1.9*	2.2*	29.435
(right arm)		0.4	0.4	0.3	0.2	
LBM	(kg)	2.6	2.6	1.8*	2.1*	36.036
(left arm)		0.4	0.3	0.3	0.2	
LBM	(kg)	22.1	21.3	16.7*	18.9*	33.610
(trunk)		2.2	2.1	2.0	1.2	
LBM	(kg)	7.8	7.3	6.1*	6.7*	18.764
(right leg)		0.8	0.7	1.0	0.6	
LBM	(kg)	7.8	7.2	6.0*	6.6*	20.708
(left leg)		0.8	0.7	1.0	0.6	
ASMI	(kg/m^2)	7.47	7.46	6.29**	6.48**	38.998
		0.41	0.47	0.66	0.27	
BFM	(kg)	16.3	18.9	15.5	14.1	2.542
(whole body)		5.4	4.6	5.1	4.8	
BFM	(kg)	1.0	1.2	1.0	0.9	1.841
(right arm)		0.4	0.4	0.4	0.4	
BFM	(kg)	1.0	1.2	1.1	0.9	1.590
(left arm)		0.4	0.4	0.4	0.4	
BFM	(kg)	8.3	9.7	7.4	6.9	2.948
(trunk)		3.2	2.5	2.7	2.8	
BFM	(kg)	2.5	2.8	2.5	2.2	2.274
(right leg)		0.7	0.7	0.8	0.6	
BFM	(kg)	2.4	2.8	2.5	2.2	2.265
(left leg)		0.7	0.7	0.8	0.6	
Total body	(kg)	36.9	35.2	29.4*	31.8*	30.656
water		3.3	2.8	2.9	2.1	

*$p < 0.05$; **$p < 0.01$ (Multiple comparisons were performed using the Dunnett's method to compare the values of the control and dynapenia, sarcopenia, or presarcopenia groups). BMI, body mass index, ASMI, appendicular skeletal mass index; LBM, lean body mass; BFM. body fat mass.
The values in the bottom row represent standard deviations.

the main effect of sarcopenia category on body composition was significant [$F_{(12)} = 28.173$, $p < 0.01$]. The dynapenia and sarcopenia groups had significantly less muscle mass in the leg than the control group. The sarcopenia group had significantly less muscle mass in the arm than the control group, whereas dynapenia group had significantly more muscle mass in the arm than the control group. Additionally, the sarcopenia group had significantly less BFM both in the arm and leg than the control group.

In men, the results of the MANOVA also showed that the main effect of sarcopenia category on body composition was significant [$F_{(12)} = 9.073$, $p < 0.01$]. The muscle mass of the sarcopenia group both in the arm and leg was less than that of the control group. However, unlike in women, no significant differences in the arm and leg muscle mass were detected between the control and dynapenia groups. Instead, BFM was higher in the leg in the dynapenia group compared to the control group.

DISCUSSION

This study focused on the differences in appendicular muscle and fat masses of the arm and leg between older adults with dynapenia, sarcopenia, or presarcopenia and normal older adults. Our results revealed significant differences in muscle mass of the leg between the control and dynapenia or sarcopenia groups in older women and in the BFM of the leg between the control and dynapenia groups in older men.

To the best of our knowledge, this study is the first to evaluate differences in muscle and fat masses for limbs among older women and men between normal individuals and those with dynapenia. A recent study involving 765 community-dwelling older adults reported that individuals with dynapenia tend to have the highest BFM among the four groups, but the sexes were not analyzed separately (8). Another study showed that older adults with dynapenia had decreased thicknesses of the

TABLE 2 | Body composition for each sarcopenia category.

(A) Women						
		Control	**Dynapenia**	**Sarcopenia**	**Presarcopenia**	***F*-value**
LBM	(kg/m^2)					
	Arm	0.72	0.76*	0.61**	0.60**	45.306
		0.10	0.09	0.09	0.07	
	Leg	2.37	2.27**	1.98**	2.05**	127.115
		0.15	0.16	0.13	0.10	
BFM	(kg/m^2)					
	Arm	0.57	0.63	0.46**	0.47**	7.726
		0.21	0.31	0.20	0.16	
	Leg	1.29	1.34	1.03**	1.10**	10.129
		0.34	0.48	0.36	0.31	
(B) Men						
		Control	**Dynapenia**	**Sarcopenia**	**Presarcopenia**	***F*-value**
LBM	(kg/m^2)					
	Arm	0.96	0.98	0.73**	0.79**	26.980
		0.11	0.12	0.12	0.07	
	Leg	2.78	2.75	2.41**	2.45**	24.523
		0.14	0.17	0.28	0.10	
BFM	(kg/m^2)					
	Arm	0.36	0.46	0.42	0.33	2.949
		0.15	0.16	0.14	0.12	
	Leg	0.88	1.08**	1.00	0.82	3.945
		0.24	0.27	0.30	0.22	

*$p < 0.05$; **$p < 0.01$ (Multiple comparisons were performed using the Dunnett's method to compare the values of the control and dynapenia, sarcopenia, or presarcopenia groups). LBM, lean body mass; BFM, body fat mass.
The values in the bottom row represent standard deviations.

rectus femoris and medial gastrocnemius muscles compared with individuals without dynapenia (7). Similarly, older adults with dynapenia show significantly decreased knee extension strength than normal older adults (11). Our data support the abovementioned findings and provide new evidence. Muscle mass in the leg measured using BIA was significantly decreased in the dynapenia group than in the control group, despite having described dynapenia with normal muscle mass, particularly in older women. This new finding suggests that low muscle mass in the leg might be overlooked in older women who are judged not to have sarcopenia on the basis of the AWGS criteria using the ASMI.

Muscle mass of the leg in older women was significantly decreased in the dynapenia group compared with that in the control group. Women have a higher prevalence of low bone mass at either skeletal site compared with bone mass in men (27). Moreover, the older the woman, the higher the prevalence of bone mass loss (27). Older women with very low bone mass demonstrated a significantly lower leg SMI than individuals with a lower bone mass; in other words, older women with low bone mass have low muscle mass (28). Our results indicate that decreased muscle mass of the lower limbs in older women should be carefully considered in dynapenia, even if it is defined as low muscle function with normal muscle mass based on ASMI.

In older men, BFM was higher in the leg in the dynapenia group than in the control group. Particularly in the leg, this finding is similar to that of a previous study showing that older adults with dynapenia have higher echo intensities in the quadriceps femoris muscles than normal older adults, demonstrating higher fat mass (11). An increase in fat infiltration within skeletal muscle in the leg leads to low muscle strength and physical performance (29–31). Our results suggest that increases in the fat mass of the leg should be viewed with caution in older men.

Our results have important implications for dynapenia. A study evaluating the quantity/quality of leg muscles reported that thigh muscle volume and fat mass were better indicators of SMI and low muscle function,

respectively (11). Furthermore, calf circumference evaluation is used to diagnose sarcopenia or SMI (32). From a clinical perspective, the present study specifically suggests strategies for preventing dynapenia separately for females and males, including increasing muscle mass and decreasing fat mass in the leg of older women and men, respectively.

This study had several limitations. First, the present study had a cross-sectional design. Further longitudinal studies are needed to ascertain whether reductions in muscle mass and increases in fat mass of the leg influence the prevalence of dynapenia, sarcopenia, and presarcopenia over time. Second, we measured walking speed only once to minimize testing stress on participants. The AWGS recommends calculating the walking speed on an average of two tests (13). Additionally, walking speed measurements showed excellent test–retest reliability (24). Therefore, the effect of the walking speed values on the results of this study might be small. Third, we have no data of older adults regarding their physical activities or the performance of other physical tests such as the 5-time chair stand test. Therefore, we could not show that the differences in body composition between the control and dynapenia groups might be because of the differences in physical activity or test performance. Fourth, this study did not examine the muscle quality of older adults with dynapenia, sarcopenia, and presarcopenia. However, we showed the difference in the body composition of the arm and leg between normal older adults and those with dynapenia. Fifth, this study did not use dual-energy X-ray absorptiometry (DXA), the gold-standard technique in analyzing body composition. BIA methods used in this study strongly correlate with DXA methods, as reported in a previous study (33). Thus, the results were considered reliable. Additionally, attention should be paid to the data obtained using different devices to measure body composition as there is a slight difference in the values acquired through different measuring devices. Finally, we did not always measure body composition in the fasting state. Although body fluid volume variance by measuring time affects the body composition of the trunk, that of the arm and leg was not affected (33). Therefore, the results for ASMI might not have been affected.

CONCLUSIONS

Older women with dynapenia had less muscle mass in the leg than normal older women. In contrast, older men with dynapenia show more fat mass in the leg than normal older men. Future longitudinal intervention studies are needed to evaluate whether increasing muscle mass in the leg among older women and decreasing fat mass in the leg among older men influence the progress of dynapenia for older adults.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Graduate School of Integrated Arts and Sciences, Hiroshima University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HJ, ST, and RT contributed to the study design, collected, and analyzed the data. All authors contributed to the article and approved the submitted version.

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Exploring Muscle Health Deterioration and Its Determinants Among Community-Dwelling Older Adults

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Background: Age-related muscle mass and function decline are critical issues that have gained attention in clinical practice and research. Nevertheless, little is known regarding the time course of muscle health progression, and its determinants during this transition should be estimated.

Methods: We enrolled community-dwelling adults aged ≥65 years during their regular health checkup. The participants' body composition and muscle function were measured annually from 2015 to 2021. Presarcopenia was characterized by the loss of muscle mass only; dynapenia was defined as low muscle function without changes in muscle mass; and sarcopenia was indicated as a decline in both muscle mass and muscle function. We observed the natural course of muscle health progression during aging. The relationship between muscle health decline and different determinants among old adults was examined.

Results: Among 568 participants, there was 18.49%, 3.52%, and 1.06% of healthy individuals transited to dynapenia, presarcopenia, and sarcopenia, respectively. Significant positive correlations between age, fat-to-muscle ratio (FMR) and the dynapenia transition were existed [hazard ratio (HR) = 1.08 and HR = 1.73, all $p < 0.05$]. Serum albumin level had negative correlation with the dynapenia transition risk (HR = 0.30, $p = 0.004$). Participants with these three risk factors had the highest HR of dynapenia transition compared to those without (HR = 8.67, $p = 0.001$). A dose-response effect existed between risk factors numbers and the risk of dynapenia transition (p for trend < 0.001). This positive association and dose-response relationship remains after multiple covariates adjustment (HR = 7.74, $p = 0.002$, p for trend < 0.001). Participants with two or more than two risk factors had a higher risk of dynapenia transition than those with low risk factors ($p = 0.0027$), and the HR was 1.96 after multiple covariate adjustment ($p = 0.029$).

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Conclusion: Healthy community-dwelling old adults tended to transit to dynapenia during muscle health deterioration. Individuals with older age, higher FMR, lower albumin level had a higher risk of dynapenia transition; and a positive dose-response effect existed among this population as well.

Keywords: sarcopenia, transition, muscle function, fat-to-muscle ratio, dynapenia

INTRODUCTION

The distressing physical challenges of advancing age include progressively decline in muscle mass and muscle function with concomitant increase in body fat, which result in adverse clinical events such as falls, fractures, functional disability, and mortality (1–3). The term sarcopenia was originally meant to represent the loss of muscle mass during aging process (4). To facilitate the precise identification of deteriorated muscle health, more definitions have been proposed. According to the consensus in 2010 European Working Group on Sarcopenia in Older People (EWGSOP), presarcopenia was defined as decreased muscle mass with intact muscle strength and physical performance, and sarcopenia was described as low muscle mass with decline in muscle strength and/or physical performance (5). In 2014, Asian Working Group for Sarcopenia (AWGS) also declared Asian consensus regarding clinical operational guidelines on sarcopenia assessment with specific cutoff values for three muscle health parameters (6). Both of muscle quantity and muscle quality are equally important in muscle health aging since then.

Nevertheless, there is plenty of evidence supporting disassociated causality between changes in muscle mass and muscle strength during aging; furthermore, it revealed that the contribution of muscle atrophy to the decline in muscle strength is relatively sparse (7, 8). In reality, Clark et al. has proposed the term "dynapenia" in 2008 to define the loss of muscle strength and muscle power during aging (9). Hence, the occurrence of muscle mass loss and muscle function decline and their impacts during aging process attracted more attention in clinical research and practice.

In addition to the decline in muscle mass and muscle strength, increased fat composition during aging was also correlated with poor muscle health, and this issue has recently acquired more attentions. Based on the 1999–2002 National Health and Nutrition Examination Survey (NHANES), Danielle R Bouchard and colleagues examined the relationship among muscle strength loss, obesity, and physical function. They suggested that dynapenic obesity was associated with poorer physical performance than obesity or dynapenia alone (10). High fat mass and low muscle strength were also correlated with impaired physical performance (11–13). Therefore, body fat composition should be taken into consideration while assessing muscle health deterioration in geriatric care.

Nonetheless, little is known about the sequential order of occurrence in muscle health changes along with aging, and the major determinants associated with this process are rarely to be explored. To investigate the time course of muscle health decline, we aimed to observe changes in muscle mass, muscle function and the risk factors including different obesity indicators among Taiwanese community-dwelling older adults. We hypothesized that muscle function decline supposed be more prevalent and earlier than muscle mass loss, and the higher obesity indicators determined the muscle health deterioration during aging process.

MATERIALS AND METHODS

Study Design and Participants

Community-dwelling old adults aged 65 years and older were enrolled in this study. They had undergone a general health checkup at the health check center in Tri-Service General Hospital (TSGH) in Taiwan from 2015 to 2021. We traced the participants and observed the parameters of skeletal muscle mass, muscle strength and physical performance annually. Participants with initial robust status transited to dynapenia, presarcopenia or sarcopenia were treated as the censoring indicator. Data were retrieved from a comprehensive questionnaire, including physical function and biological indicators. Participants with the following conditions were excluded: chest or joint pain during exercise; cognitive impairment; history of heart failure; current history of cancer under treatment; history of renal failure under regular hemodialysis; and exercise not recommended by physicians. Based on the revised Helsinki Declaration, the Institutional Review Board (IRB) of TSGH approved this study. Informed consent was obtained from all the participants.

Measurement of Muscle Strength, Physical Performance and Muscle Mass

The handgrip strength of the dominant hand was assessed with a handheld dynamometer. The time required by the participants to walk 6 m at the usual pace was recorded by a handheld chronograph, and gait speed was calculated. Eight-electrode bioelectrical impedance analysis (BIA, InBody720, Biospace, Seoul, South Korea) (14) was applied to measure appendicular skeletal muscle mass (ASM), and height-adjusted skeletal muscle mass (ASM/m^2) was calculated to define the skeletal muscle mass index (SMI).

Measurement of Obesity Profiles

Clinical measurements are all followed by standard recommended procedures. Body mass index (BMI) was defined as body weight in kilograms divided by body height in square meters (kg/m^2). Waist circumference (WC) was measured at the mid-level between the lowest costal margin and the highest border of iliac crest when the participant in the standing position. Body fat mass and body fat percentage were measured by BIA (14). Body fat mass divided by body skeletal muscle mass was calculated as the fat-to-muscle ratio (FMR).

TABLE 1 | Characteristics of participants from robust transition to dynapenia, presarcopenia and sarcopenia.

	Transition status				
Initial status	**Robust**	**Dynapenia**	**Presarcopenia**	**Sarcopenia**	
Robust	***n* = 437**	***n* = 105**	***n* = 20**	***n* = 6**	
(N = 568)	**76.94%**	**18.49%**	**3.52%**	**1.06%**	
Continuous variables[a]					***p*-value**
Age (years)	69.5 ± 5.0	72.3 ± 6.1	72.9 ± 7.1	66.8 ± 6.4	< 0.001
WC(cm)	82.6 ± 9.1	82.9 ± 8.1	76.3 ± 8.9	79.8 ± 5.2	0.014
BMI (kg/m^2)	25.12 ± 3.08	25.58 ± 2.61	22.78 ± 2.58	23.42 ± 1.54	0.001
SMI (kg/m^2)	7.15 ± 0.92	7.16 ± 0.91	6.54 ± 0.85	6.66 ± 0.72	0.018
Grip strength (kg)	30.8 ± 8.8	29.1 ± 8.4	28.7 ± 8.4	29.2 ± 9.5	0.259
Gait speed (m/s)	1.32 ± 0.25	1.27 ± 0.21	1.42 ± 0.26	1.31 ± 0.18	0.076
Fat mass (kg)	19.7 ± 6.1	21.0 ± 5.6	16.1 ± 4.8	16.7 ± 4.7	0.004
Body fat (%)	29.9 ± 7.4	31.4 ± 6.9	27.8 ± 6.4	28.0 ± 7.9	0.107
FMR	0.82 ± 0.32	0.89 ± 0.30	0.73 ± 0.24	0.75 ± 0.31	0.123
PA (kcal/week)	10411.0 ± 3586.1	8507.3 ± 2670.8	8419.7 ± 3534.6	9011.0 ± 3598.1	0.002
WBC counts (/ul)	5721 ± 1413	5851 ± 1417	5363 ± 1380	6187 ± 1360	0.497
Hemoglobin (g/dl)	14.0 ± 1.1	13.7 ± 1.3	13.4 ± 0.8	14.6. ± 0.1	0.063
Creatinine (mg/dl)	0.90 ± 0.59	0.94 ± 0.73	0.88 ± 0.22	0.72 ± 0.22	0.867
LDL (mg/dl)	110.5 ± 30.7	104.0 ± 26.1	101.1 ± 27.7	126.0 ± 23.9	0.110
Albumin (mg/dl)	4.34 ± 0.21	4.28 ± 0.25	4.24 ± 0.30	4.38 ± 0.16	0.028
Categorical variables [b]					
Male	225 (51.5)	47 (44.8)	8 (40.0)	3 (50.0)	0.506
Smoking	102 (23.3)	21 (20.0)	2 (10.0)	2 (33.3)	0.441
AC ≥ 1 time/week	43 (9.8)	14 (13.3)	2 (10.0)	1 (16.7)	0.704
Hypertension	146 (33.4)	41 (39.0)	5 (25.0)	1 (16.7)	0.432
DM	41 (9.4)	14 (13.3)	2 (10.0)	1 (16.7)	0.607
Stroke	6 (1.4)	2 (1.9)	0	0	0.906
CAD	19 (4.3)	8 (7.6)	0	0	0.349
COPD	12 (2.7)	6 (5.7)	2 (10.0)	2 (33.3)	0.023
Arthritis	57(13.0)	19 (18.1)	4 (20.0)	2 (33.3)	0.224

AC, alcohol consumption; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FMR, fat-to-muscle ratio; PA, physical activity; LDL, low-density lipoprotein; SMI, skeletal muscle mass index; WBC, white blood cell; WC, waist circumference.

[a] *Values in the continuous variables were expressed as mean ± standard deviation.*

[b] *Values in the categorical variables were expressed as number (percent).*

Definitions of Dynapenia, Presarcopenia, and Sarcopenia

The cutoff points of low SMI, low handgrip strength and slow gait speed were determined according to the 2019 AWGS consensus (15). Sarcopenia was defined as low SMI plus low handgrip strength and/or slow gait speed. Presarcopenia was defined as low SMI without a decline in handgrip strength or gait speed. Dynapenia was defined as low handgrip strength and/or slow gait speed without low SMI.

Covariates Measurement

Age, sex, smoking status, alcohol consumption, and medical history were collected from a self-completed questionnaire and health insurance card. Past history, including hypertension, diabetes mellitus (DM), stroke, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and arthritis, was obtained by self-report of a doctor's diagnosis. We applied the Chinese version of the International Physical Activity Questionnaire (IPAQ) for physical activity evaluation (16). After the patients fasted for 8 h, blood samples were collected. White blood cell counts, hemoglobin, serum low-density lipoprotein cholesterol (LDL), serum creatinine, and serum albumin levels were analyzed.

Statistical Analysis

Statistical analyses were performed with SPSS (Version 18.0 for Windows; SPSS Inc.). We calculated the mean ± standard

deviation values for each continuous variable and numbers (percentages) for categorical variables. The transition rates from robust to dynapenia, presarcopenia and sarcopenia were calculated. The covariates with significant hazard ratio to increase the risk from robust transition to dynapenia were determined by Cox regression analysis. In addition to the possible confounding factors such as age, sex, chronic diseases, physical activity and nutrition related biomarkers, we especially focused on different fat indices including BMI, WC, fat mass, body fat percentage and FMR to investigate their impact on muscle health deterioration. The cutoff point of the high risk factor with significant hazard ratio to predict dynapenia transition was determined by using receiver operating characteristic (ROC) analysis. Kaplan–Meier analysis was applied to ascertain the relation of high/low risk factor and the cumulative hazard of transition to dynapenia. The effects of cluster risk factors compared to no risk factor on dynapenia transition were analyzed by multiple covariates Cox regression. To determine the effects of high risk factors on the risk prediction of dynapenia transition, the extended model approach with stepwise variable adjustment by Cox proportional hazards regression was conducted as follows: Model 1 = sex, smoking, alcohol consumption; Model 2 = Model 1 + hypertension, DM, stroke, CAD, COPD, arthritis; Model 3 = Model 2 + physical activity, WBC counts, hemoglobin, serum creatinine, LDL

TABLE 2 | Hazard of covariates in participants transition from robust to dynapenia.

	Hazard ratio (95% confidence interval)	*p*-Value
Age	1.08 (1.05–1.11)	< 0.001
Sex	0.86 (0.58–1.27)	0.464
smoking	0.97 (0.60–1.57)	0.917
AC ≥ 1 time/week	1.47 (0.83–2.58)	0.182
Hypertension	1.34 (0.90–2.00)	0.143
DM	1.45 (0.82–2.55)	0.199
Stroke	1.50 (0.37–6.11)	0.566
CAD	1.85 (0.90–3.82)	0.093
COPD	1.68 (0.73–3.85)	0.214
Arthritis	1.29 (0.78–2.12)	0.318
Body mass index	1.06 (0.99–1.13)	0.058
Waist circumference	1.01 (0.98–1.03)	0.355
Fat mass	1.04 (1.01–1.07)	0.021
Body fat percentage	1.03 (1.01–1.05)	0.034
FMR	1.73 (1.05–2.84)	0.029
White blood cell counts	1.13 (0.98–1.29)	0.086
Hemoglobin	0.89 (0.72–1.09)	0.272
Serum creatinine	1.11 (0.86–1.41)	0.426
LDL	0.99 (0.98–1.00)	0.088
Albumin	0.30 (0.13–0.67)	0.004

AC, alcohol consumption; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FMR, fat-to-muscle ratio; LDL, low-density lipoprotein.

RESULTS

Demographics of Participants by Robust Progression to Dynapenia, Presarcopenia, and Sarcopenia

The demographics of the 568 subjects by transition status are presented in **Table 1**. The mean age was 70.09 ± 5.46 years, and 49.82% (n = 283) of the participants were male. During the 6-year follow-up period, 18.49% (n = 105), 3.52% (n = 20), and 1.06% (n = 6) of individuals transited to dynapenia, presarcopenia, and sarcopenia, respectively. The mean time of transition to dynapenia was 63.93 ± 18.97 months, to sarcopenia was 71.46 ± 5.27 months, to presarcopenia was 70.43 ± 8.45months. There were significant differences among the transitional statuses in age, WC, BMI, SMI, fat mass, physical activity, albumin, and history of COPD. Individuals who transited to dynapenia were tended to be older and had a higher obesity profile (BMI, WC, fat mass, body fat percentage, and FMR) as well as a lower albumin level.

Association Between Covariates and the Risk of Transition to Dynapenia

Age, fat mass, body fat percentage, and FMR showed significant positive correlations with the risk of transition to dynapenia [Hazard ratio (HR) = 1.08, 95% confidence interval (CI) = 1.05–1.11, $p < 0.001$; HR = 1.04, 95%CI = 1.01–1.07, $p = 0.021$; HR = 1.03, 95%CI = 1.01–1.05, $p = 0.034$; and HR = 1.73, 95%CI = 1.05–2.84, $p = 0.029$, respectively). Serum albumin level had significant negative correlation with the risk of dynapenia

TABLE 3 | Hazard ratio of cluster risks to predict participants transition from robust to dynapenia.

	Hazard ratio (95% confidence interval)	*p*-Value	*p* for trend
Model 1			
No risk factor	Reference		<0.001
1 Risk factor	3.22 (0.93–11.08)	0.064	
2 Risk factors	3.72 (1.10–12.56)	0.034	
3 Risk factors	8.67 (2.50–30.04)	0.001	
Model 2			
No risk factor	Reference		<0.001
1 Risk factor	2.93 (0.84–10.14)	0.091	
2 Risk factors	3.44 (1.01–11.67)	0.048	
3 Risk factors	7.84 (2.23–27.43)	0.001	
Model 3			
No risk factor	Reference		<0.001
1 Risk factor	2.90 (0.82–10.13)	0.096	
2 Risk factors	3.25 (0.92–11.37)	0.065	
3 Risk factors	7.74 (2.16–27.58)	0.002	

Model 1 = sex, smoking, AC.
Model 2 = Model 1 + hypertension, DM, stroke, CAD, COPD, arthritis.
Model 3 = Model 2 + PA, WBC counts, Hemoglobin, serum creatinine, LDL.
AC, alcohol consumption; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PA, physical activity; LDL, low-density lipoprotein; WBC, white blood cell.

transition (HR = 0.30, 95%CI = 0.13–0.67, $p = 0.004$). However, the relationships between BMI and WC and the risk of transition to dynapenia were insignificant (**Table 2**). Among the obesity parameters, FMR had the highest HR of dynapenia transition, and the optimal cutoff value of FMR for this risk prediction was 0.863 by using ROC analysis. The optimal cutoff point of age to estimate dynapenia transition was 68.5 years old, and the optimal cutoff value of serum albumin was 4.35mg/dl. Participants with an older age, high FMR and low albumin level were defined accordingly for further analysis.

Association Between Cluster of Risk Factors and the Risk of Transition to Dynapenia

Older age, higher FMR and lower albumin level were taken into account as risk factors to predict dynapenia transition. There were 540 participants with complete data of these three parameters enrolled for subgroup analysis. Participants with three risk factors had the highest HR of dynapenia transition compared to the participants with no risk factor (HR = 8.67, 95%CI = 2.50–30.04, $p = 0.001$) (**Table 3**). A dose-response effect was noted between risk factors numbers and the risk of dynapenia transition (p for trend < 0.001). The positive association remains after further adjustment with multiple covariates (HR = 7.74, 95%CI = 2.16–27.58, $p = 0.002$). And the dose-response relationship between numbers of risk factors and the transition risk to dynapenia still unchanged (p for trend < 0.001).

Cumulative Risk of Transition to Dynapenia Between High Risk Factor and Low Risk Factor

Participants with two or more than two risk factors of dynapenia transition were defined as high risk factors. **Figure 1** shows the Kaplan–Meier analysis to estimate the 78 months of cumulative hazard on transition to dynapenia by high and low risk factors. Participants with high risk factors had a higher risk of transition to dynapenia than those with low risk factors ($p = 0.0027$).

The Risk of Transition to Dynapenia by High Risk Factor

Multiple covariate Cox regression analysis was performed to examine the association of high risk factors and the risk of transition to dynapenia (**Table 4**). After multiple covariate adjustment, the HR of transition to dynapenia for participants with high risk factors was 1.96 (95%CI = 1.07–3.59, $p = 0.029$).

DISCUSSION

Among the community-dwelling older people included in this study, 76.94% remained healthy with good muscle mass and muscle function at the 6-year follow-up. Regarding individuals with muscle health progression, 18.49% of old adults transited to dynapenia, followed by presarcopenia (3.52%) and sarcopenia (1.06%). The analyses suggested that participants had more problems in terms of muscle strength decline rather than muscle mass loss during aging process, which was consistent with the findings of some longitudinal studies (9, 17, 18). For example, Visser M and colleagues found that participants had a greater decrease in knee extensor strength than in the mid-thigh muscle cross-sectional area (CSA) in both sexes in a 2.5-year longitudinal study (19). Delmonico et al. observed that there were 9 and 3.2% reductions in the total thigh area among men and women during a 5-year follow-up; nevertheless, the loss of average maximal muscle torque was much greater than the total thigh area, with 16.1% in men and 13.4% in women (18). Clark et al. investigated muscle mass and knee extensor strength among elderly individuals in a 6-year cohort study and showed that participants with different annual rates of muscle strength decline had similar amounts of muscle mass loss (9). According to the study by Murphy et al., gait speed and handgrip strength decline before the loss of appendicular lean mass during the transition from healthy muscle conditions to sarcopenia state (20). Based on a 12-year follow-up cohort study, Frontera et al. found a much greater decrease of 20–30% in knee and elbow isokinetic muscle strength than the loss of 10–15% in mid-thigh muscle CSA among older men (17). To the best of our knowledge, studies applying the cutoff point of low muscle mass, low muscle strength and slow gait speed in light of the EWGSOP or AWGS consensus are scarce. For a more comprehensive survey, we used the latest AWGS consensus to define low muscle function and low muscle mass for observing muscle health deterioration from robust to dynapenia, presarcopenia, and sarcopenia.

In addition to muscle function decline, we found that individuals who transited to dynapenia had a higher obesity profile. This result was in line with that of a cross-sectional study, which suggested that older adults with a higher body fat percentage tend to have a lower handgrip strength and walking speed than those with a lower body fat percentage (21). In addition, declines in handgrip strength and gait speed accelerate while fat mass increases in people aged 70–75 years (22). This result was also supported by our earlier report that handgrip strength and gait speed decreased as FMR and body fat percentage increased in elderly individuals (23). Studies concerning the relationship between other obesity indicators and muscle function showed similar outcomes. A negative correlation was observed between WC and handgrip strength in a Taiwanese cohort study (24). Individuals with obesity at 20–50 years of age (defined by BMI $\geq$ 30 kg/m^2) were associated with low handgrip strength (25). The consistent findings across past studies using various methods for obesity and muscle strength measurement are remarkable and lend support for the findings of the present study. The novelty of our research was the application of the latest AWGS cutoff points for low muscle strength and low muscle mass. To the best of our knowledge, this is the first longitudinal study comparing multiple obesity indicators during the natural course of muscle health transition to dynapenia, presarcopenia and sarcopenia.

In our study, the correlations between BMI, WC and the transition to dynapenia were insignificant. Skeletal muscle mass may decrease by up to 40% between 20 and 70 years of age, and fat mass will increase to a peak gradually at the age of 60–70;

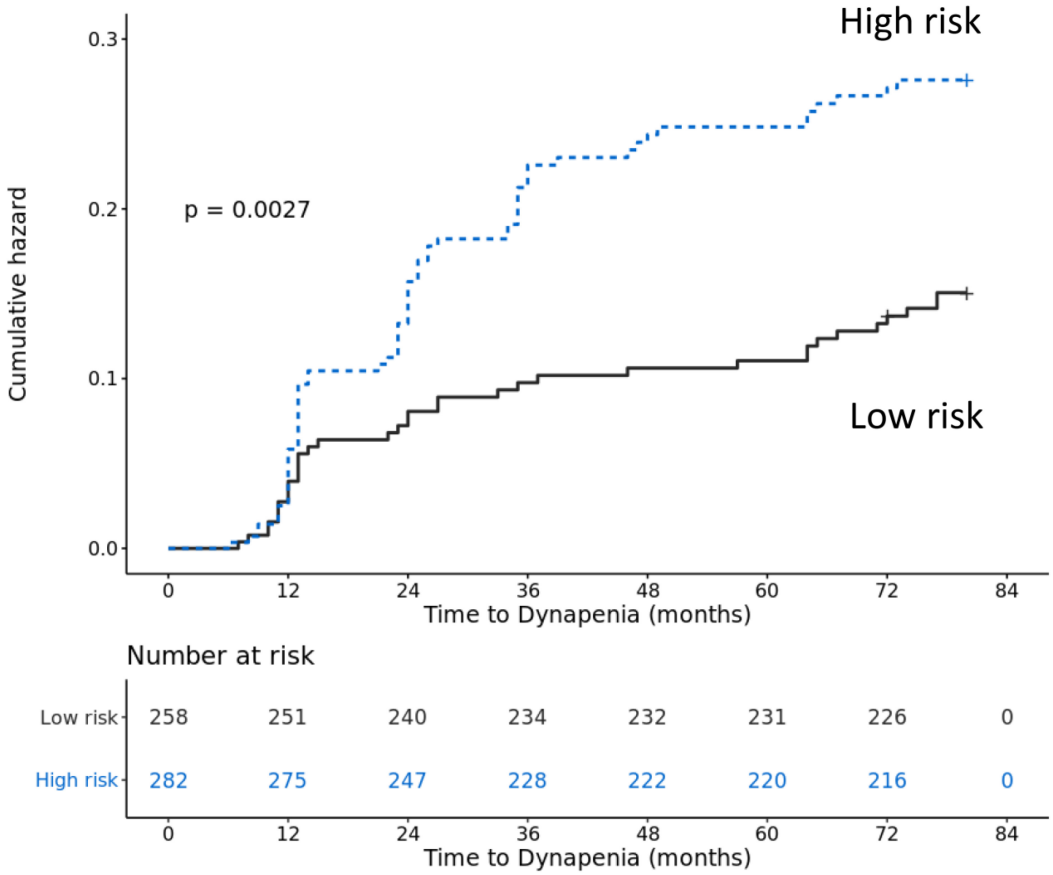

FIGURE 1 | Accumulative risk of transition to dynapenia from robust between participants with high risk factors and low risk factors.

then, fat mass and fat-free mass will decline simultaneously later in life (26–28). Older individuals tend to have greater amounts of visceral fat than younger subjects despite having the same WC (29). It was also suggested that BMI is an imperfect fat index for older adults in research (30). Using BMI and WC as fat indicators may be masked by body composition changes during aging. These could partially explain the insignificant findings of the correlations between BMI, WC and the transition to dynapenia.

On the other hand, significantly positive correlations existed between fat mass, FMR, body fat percentage and the transition to dynapenia. This result suggested that taking fat components into consideration is important when evaluating muscle strength and gait speed deterioration. Among the fat indicators, FMR was found to be the best predictor for the risk of transition to dynapenia. Lee HS et al. also explored that FMR was negatively correlated with handgrip strength in both sexes, and participants in the highest FMR quartile had lower handgrip strength among 55- to 65-year-old patients undergoing hemodialysis in Korea (31). According to the study by Sternfeld et al., the lean-to-fat ratio was positively associated with walking speed among community-dwelling participants aged 55 years and older in California (32). In their opinion, muscle strength or function could be assessed more precisely by considering body fat, and this concept was in accordance with our results. Similarly, the two abovementioned studies both applied BIA and calculated the ratio of body fat mass to muscle mass. The two studies focused on the correlations of FMR with physical performance, cardiac events, and all-cause mortality. In contrast, our study emphasized the relationship between obesity indicators and the natural course of muscle health transition. Moreover, we applied AWGS cutoff points to define low muscle quantity and low muscle quality. In this context, the FMR, which simultaneously considers muscle mass and fat mass, may provide a more suitable surrogate for estimating muscle health transition to dynapenia.

TABLE 4 | Hazard ratio of transition from robust to dynapenia in participants with high risk factors.

	Hazard ratio (95% confidence interval)	*p*-Value
Model 1	2.06 (1.17–3.64)	0.012
Model 2	2.01 (1.12–3.57)	0.018
Model 3	1.96 (1.07–3.59)	0.029

Model 1 = sex, smoking, AC.
Model 2 = Model 1 + hypertension, DM, stroke, CAD, COPD, arthritis.
Model 3 = Model 2 + PA, WBC counts, Hemoglobin, serum creatinine, LDL.
AC, alcohol consumption; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PA, physical activity; LDL, low-density lipoprotein; WBC, white blood cell.

Previous literature also provided a possible mechanism linking fat infiltration into the muscle, muscle function decline, and metabolic disarrangement (33). Intermuscular and intramuscular fat accretion coincides with aging and obesity and may be associated with deleterious health events (18, 34, 35). The infiltrated fat may induce lipotoxicity, which is crucial in the development of peripheral insulin resistance during the aging process (35–37). Muscle contraction leads to energy depletion and stimulates 5′-adenosine monophosphate-activated protein kinase (AMPK) activity to facilitate ATP synthesis (38, 39). Obesity suppresses AMPK activity (40), promoting fast-to-slow muscle fiber transformation, which can affect energy use and contractile function (41, 42). Obesity is also related to increases in pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (43). These cytokines are associated with lower muscle mass and strength in the elderly, and the possible mechanism may be muscle protein catabolism and inhibiting muscle protein synthesis (44). In summary, obesity and fatty deposits in the muscle directly induce inflammation, which in turn negatively interferes with muscle strength (43).

In addition to older age and adiposity, we also explored that low albumin level increased the risk of dynapenia transition. Protein synthesis with energy production is necessary for muscle strength generation. Older people with malnutrition will increase the risk of frailty, disability and mortality. Some study results are consistent with our research findings. Schalk et al. explored that lower serum albumin level was cross-sectionally associated with handgrip strength decline at baseline in both genders with age of 65–88 years old. After adjustment with multiple confounders, the substantial negative relationship remained between low serum albumin concentration and handgrip strength over 3- and 6-year follow up (45).

In a prospective cohort study from community-dwelling people aged 55 and older over with 3–5 years follow-up, it revealed that older adults with low concentration of serum albumin will decrease 37% in gait speed and 91% in timed-up-and-go test (46). To sum up, malnutrition represented by low serum albumin level is an optimal surrogate to predict muscle function transition from robust to dynapenia.

In our study, older age, high FMR and low serum albumin level were the three risk factors leading to increase the risk of muscle health transition from robust to dynapenia. A significant dose-response effect existed between cluster factors and the risk of dynapenia transition. In general, older adults with two or more than two of these factors will increase the dynapenia transition risk than those without. This is the first study to composite the possible risk factors in predicting dynapenia transition among older people.

The strength of this study is that we explored the muscle function decline occurred earlier than muscle mass loss during aging process; older age, adiposity, and malnutrition were implicated with this transition. Few studies have reported the deteriorating effect of obesity on muscle strength (47). To the best of our knowledge, this is the first study that presented the correlations between different obesity indicators and the transition to dynapenia, presarcopenia and sarcopenia. We used AWGS cutoff points to categorize the transition status in a longitudinal study rather than observing changes in single muscle health parameters. By jointly using age, FMR and serum albumin level, we present a cost-efficient and convenient way to predict the risk of dynapenia transition in clinical practice.

Some limitations in this study should be acknowledged. First, the data were retrieved from community-dwelling elderly individuals in Taiwan, and the generalizability of our results to other populations may be limited. Second, applying BIA for body composition estimation is not a standard method. However, adequate hydration and exclusion of severe obesity cases were performed in our study to obtain reliable results. Last, intramuscular or intermuscular fat was difficult to accurately quantify by BIA. Nevertheless, FMR, measured by BIA in this study, reflects fat and muscle distribution and is a better predictor of muscle function decline.

In conclusion, we disclosed that muscle function decline was more prevalent and earlier than muscle mass loss during aging process. Older age, obesity and poor nutrition were risk factors for healthy old people on dynapenia transition. A dose-response effect existed between these three factors and the risk of transition from robust to dynapenia. Older adults with two or more than two of these factors will increase the risk of dynapenia transition than those without.

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 Institution Review Board, Tri-Service General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

T-WK designed the study, analyzed and interpreted the data, and revised the manuscript. Y-PC contributed to manuscript writing. W-HF contributed to perform the statistical analysis and data interpretation. W-LC conceived the study design, participant recruitment, data acquisition, and interpretation. W-SY contributed to study design and data interpretation. T-CP contributed to data acquisition. All authors contributed to the article and approved the submitted version.

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Evaluation of a Fully Automatic Deep Learning-Based Method for the Measurement of Psoas Muscle Area

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Background: Manual muscle mass assessment based on Computed Tomography (CT) scans is recognized as a good marker for malnutrition, sarcopenia, and adverse outcomes. However, manual muscle mass analysis is cumbersome and time consuming. An accurate fully automated method is needed. In this study, we evaluate if manual psoas annotation can be substituted by a fully automatic deep learning-based method.

Methods: This study included a cohort of 583 patients with severe aortic valve stenosis planned to undergo Transcatheter Aortic Valve Replacement (TAVR). Psoas muscle area was annotated manually on the CT scan at the height of lumbar vertebra 3 (L3). The deep learning-based method mimics this approach by first determining the L3 level and subsequently segmenting the psoas at that level. The fully automatic approach was evaluated as well as segmentation and slice selection, using average bias 95% limits of agreement, Intraclass Correlation Coefficient (ICC) and within-subject Coefficient of Variation (CV). To evaluate performance of the slice selection visual inspection was performed. To evaluate segmentation Dice index was computed between the manual and automatic segmentations (0 = no overlap, 1 = perfect overlap).

Results: Included patients had a mean age of 81 ± 6 and 45% was female. The fully automatic method showed a bias and limits of agreement of −0.69 [−6.60 to 5.23] cm^2, an ICC of 0.78 [95% CI: 0.74–0.82] and a within-subject CV of 11.2% [95% CI: 10.2–12.2]. For slice selection, 84% of the selections were on the same vertebra between methods, bias and limits of agreement was 3.4 [−24.5 to 31.4] mm. The Dice index

for segmentation was 0.93 ± 0.04, bias and limits of agreement was −0.55 [1.71–2.80] cm^2.

Conclusion: Fully automatic assessment of psoas muscle area demonstrates accurate performance at the L3 level in CT images. It is a reliable tool that offers great opportunities for analysis in large scale studies and in clinical applications.

Keywords: computed tomography, muscle assessment, artificial intelligence, psoas muscle area (PMA), body composition, sarcopenia

INTRODUCTION

Low muscle mass is a key criteria for diagnoses of malnutrition and sarcopenia (1, 2). It furthermore is a predictor for functional decline, falls, rehospitalization and higher mortality rates at mid-term to long-term follow-up (3). When low muscle mass is diagnosed timely, nutrition and exercise interventions can be implemented to mitigate muscle loss and subsequently improve clinical prognosis (4, 5). The gold standard for determination of muscle mass is the measurement of muscle area on the Computed Tomography (CT) scan (6). CT scans are frequently available in daily clinical practice, but muscle mass measurement for clinical assessment is currently not performed. A limiting factor is the processing method, which requires both expertise and time (7). Therefore, for clinical implementation and large-scale clinical outcome studies a fully automatic method is an unmet need.

Typically, muscle mass is assessed with proxy measures such as total muscle area or psoas muscle area determined in a single axial slice at level of lumbar vertebra 3 (L3) (6, 8). Both are highly correlated with total body muscle mass (9). Furthermore, the two areas show a good predictive ability for various clinical outcomes including major surgical complications, quality of life and mortality (6). It takes two steps to calculate total muscle area or psoas muscle area on an axial slice. First, the correct slice has to be selected and second, the muscle area of interest has to be identified, a process which is known as segmentation (10). Currently both processes are performed manually by trained researchers requiring approximately 5 min for slice selection and 10 min for segmentation per scan (6, 11).

Due to continuous improvements in medical image analysis, deep learning-based methods are able to replace the cumbersome manual process of slice selection and segmentation (12). Several studies have shown promising results for the automatic segmentation of muscle area on a single axial slice of the CT scan (12–15). However, validated fully automatic methods performing slice selection as well as segmentation is still lacking. The main purpose of this study is to evaluate slice selection and segmentation of the psoas muscle area on the CT scan of a fully automatic deep learning method compared to a manual method.

MATERIALS AND METHODS

Study-Cohort

For this study, data of all patients with severe aortic stenosis that were planned to undergo Transcatheter Aortic Valve Replacement (TAVR) from January 2010 to January 2016 were used ($n = 651$) (16). All patients provided informed consent for the procedure. The institutional review board approved this study with a waiver. The protocol was in accordance with the declaration of Helsinki.

Data Collection

All patients underwent a CT scan prior to TAVR, with a 64-slice multi-detector scanner (Brilliance, Philips Medical Systems, Cleveland, OH) or a dual source 2 × 192 slice multi-detector scanner (Somatom Force, Siemens, Erlangen, Germany) after intravenous contrast administration. A body scan from cranium to thighs was acquired and reconstructed with at a slice thickness of 1.5 or 3.0 mm. A more detailed description of the method is provided elsewhere (16). Patient characteristics were collected from the prospective Institutional TAVR registry.

Manual Psoas Measurement

Manual assessment of the psoas muscle area had been previously performed by Van Mourik et al. (16). In short, slices were selected manually in the middle of L3, at the rear end of the vertebral body, using a multiplanar view on the Sante DICOM viewer (version 5.0.4, Santesoft, Athens, Greece). For segmentation Slice-O-Matic software (version 5.0, TomoVision, Montreal, Quebec, Canada) was used. Psoas muscle area was manually segmented with a mouse-operated paint brush selecting pixels with HU values between −29 and 150. Complete segmentation was performed by one researcher (YJ), trained in segmentation of psoas muscle area, blinded for patient characteristics.

Automatic Psoas Measurement

The automatic assessment was performed by the deep learning-based software of Quantib Body Composition (version 0.1.0, Quantib, Rotterdam, Netherlands) (17). The Quantib Body Composition software is available online for testing[1] and provides quantification of three muscle areas: psoas muscle, abdominal muscle, long spine muscle, and two fat tissues: visceral fat and subcutaneous fat. Furthermore, features can be calculated from these segmentations such as skeletal muscle density (SMD) or intramuscular adipose tissue (IMAT). The algorithm allows post-hoc decisions for selection thresholds of Hounsfield Units (HU). The narrow field of view in several CT images only allowed accurate measurements of the psoas muscle in this cohort.

The software first resampled CT scans to 5 mm slice thickness. Based on these resampled slices, the L3 slice was automatically

[1]Research.quantib.com

TABLE 1 | Patient characteristics.

	Total ($n = 583$)	Male ($n = 264$)	Female ($n = 319$)
Age, years, mean ± SD	81 ± 7	81 ± 7	81 ± 8
Height, cm, mean ± SD ($n = 582$)	167 ± 9	174 ± 7	161 ± 7
Weight, kg, mean ± SD	77 ± 15	81 ± 14	73 ± 15
BMI, kg/m^2, mean ± SD	27.5 ± 4.9	26.8 ± 4.0	28.1 ± 5.5
Underweight BMI < 18.5, *n* (%)	5 (1)	2 (1)	3 (1)
Normal BMI > 18.5 and < 25, *n* (%)	186 (32)	91 (34)	95 (30)
Overweight BMI > 25 and < 30, *n*%	247 (42)	123 (47)	124 (39)
Obese BMI > 30, *n*%	145 (25)	48 (14)	97 (30)
BSA, m^2, mean ± SD ($n = 582$)	1.9 ± 0.2	2.0 ± 0.2	1.8 ± 0.2
NYHA, III/IV, *n* (%)	411 (70)	185 (70)	226 (71)
Diabetes mellitus, *n* (%) ($n = 582$)	175 (30)	87 (33)	88 (28)
PAD, yes, *n* (%)	157 (27)	94 (36)	63 (20)
COPD, yes, *n* (%)	190 (33)	97 (37)	93 (29)
Albumin, g/L, mean ± SD ($n = 480$)	42 ± 4	42 ± 4	42 ± 4
Hemoglobin, mmol/L, Mean ± SD ($n = 580$)	7.9 ± 1.0	8.0 ± 1.1	7.7 ± 0.9
eGFR, mL/min/1.73 m2, mean ± SD ($n = 578$)	66 ± 23	65 ± 23	66 ± 23
STS-riskscore,%, mean ± SD ($n = 582$)	5.3 ± 3.3	5.2 ± 3.4	5.4 ± 3.2
Euroscore II (%), mean ± SD	5.5 ± 4.2	6.3 ± 4.9	4.9 ± 3.4
Left ventricular ejection fraction < 45%, *n* (%), ($n = 582$)	108 (19)	69 (26)	39 (12)
Aortic valve area (cm2), mean ± SD ($n = 540$)	0.82 ± 0.29	0.84 ± 0.20	0.81 ± 0.34
Aortic valve peak gradient (mmHg), mean ± SD ($n = 562$)	68 ± 23	68 ± 22	69 ± 24

SD, standard deviation; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; STS, society of thoracic surgeons; PAD, peripheral arterial disease; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease.

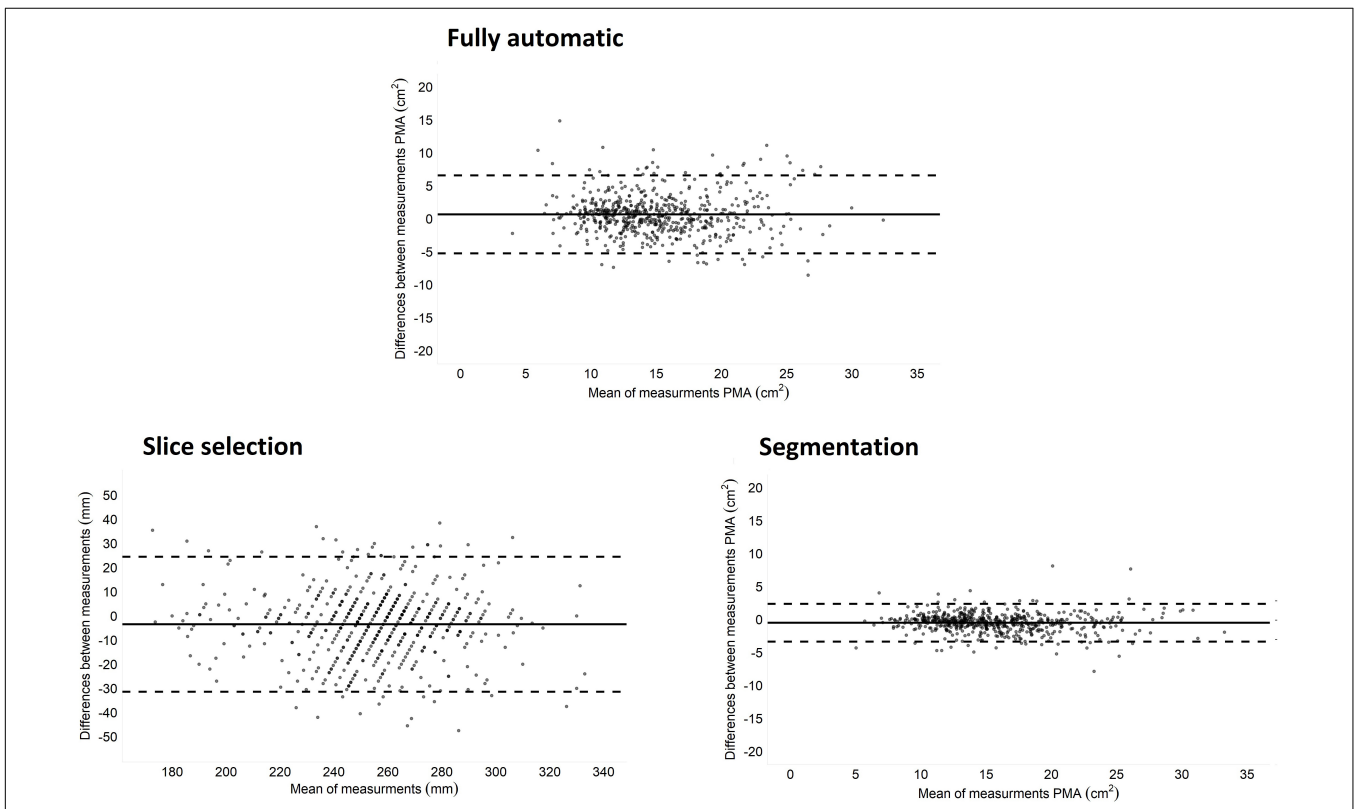

FIGURE 1 | Bland-Altman plots of difference between the manual and automatic method. Fully automatic is automatic slice selection followed by automatic segmentation compared to complete manual slice selection and segmentation. Slice selection is automatic versus manual slice selection. Segmentation is automatic versus manual segmentation on the manual selected slice.

selected using a convolutional neural network. Subsequently, segmentation of the muscle and fat area was performed in the selected slice using a second convolutional neural network. To limit the influence of the automatic selection, results were averaged over 5 slices, i.e., 25 mm. Boundaries in Hounsfield Units (HU) between 29 and 150 HU were used for selection of muscle tissue. As output the program provided area of the muscle area and fat area in squared centimeters.

All automatically selected slices as well as all automatically segmented muscles were visually inspected. Three random examples and the three biggest outliers, based on the within-subject Coefficient of Variation (CV) for segmentation and distance from reference for slice selection, are shown and discussed in the result section. The examples and outliers are used as case examples to give an overview of the performance of the Quantib software compared to manual slice selection and segmentation.

Statistical Analysis

Data of continuous variables were presented as mean ± standard deviation or median and Inter Quartile Range (IQR) depending on distribution. Categorical variables were reported as a frequency and percentage.

The area of the psoas muscle attained with automatic method was compared with the manual method using the mean or median difference, the average bias and 95% limits of agreement, the two-way mixed ICC, the within-subject CV (18), and Bland-Altman analysis (19). Additionally, to get insight into the performance of the method's two components, the slice selection and segmentation were evaluated separately. Detailed comparison between automatic and manual slice selection was performed with visual inspection by one author (DvE) to determine the number of scans that were not on the same vertebra. Comparison of segmentation was performed using the Dice index, a metric that describes overlap between the two segmentations (0 = no overlap, 1 = perfect overlap). For evaluation of the segmentation the manually selected slices were used.

To investigate the method's performance, the evaluation is furthermore shown between sexes and for different Body Mass Index (BMI) categories (normal/underweight: BMI = 25, overweight BMI > 25 and = 30 or obese BMI > 30) (13). Differences between groups were calculated with student *t*-test or one-way ANOVA and Tukey's tests. Significance level was set at $p < 0.05$ and all analysis were performed in R statistical software version 3.6.0.

RESULTS

Study Cohort

Of the 651 patients undergoing TAVR, 68 patients were excluded, 36 patients had no CT in their medical records, in 15 patients the lumbar section was not available on the scan, 12 patients had no full body scan at 1.5 or 3 mm and 5 patients had an unusable scan at L3 due to noise or artifacts. The remaining 583 patients had a mean age of 81 ± 6 year and 45% was female. A comprehensive list of patient characteristics is shown in **Table 1**.

Evaluation of Psoas Measurement

In the fully automatic method, i.e., automatic slice selection followed by automatic segmentation, the average measured psoas muscle area was 15.4 ± 4.6 cm^2 for the manual method and 14.7 ± 4.7 cm^2 for the automatic method. Median difference was 1.54 cm^2 [IQR: 0.78–2.96], and Bland-Altman analysis (**Figure 1**) showed a bias of −0.69 cm^2 with a 95% limit of agreement of −6.60 to –5.23 cm^2. The fully automatic muscle assessment had an ICC of 0.78 [95% CI: 0.74–0.82] and a within-subject CV of 11.2% [95% CI: 10.2–12.2]. Male patients had a significantly lower within-subject CV than female patients, 10.0% [8.6–11.4] vs. 12.2% [10.8–13.6] ($p = 0.03$). No significant differences were seen among the BMI groups.

Evaluation of L3 Slice Selection

Median difference in slice selection was 7.5 mm [IQR: 3.0–16.5] and the bias was 3.4 mm with 95% limits of agreement of −24.5

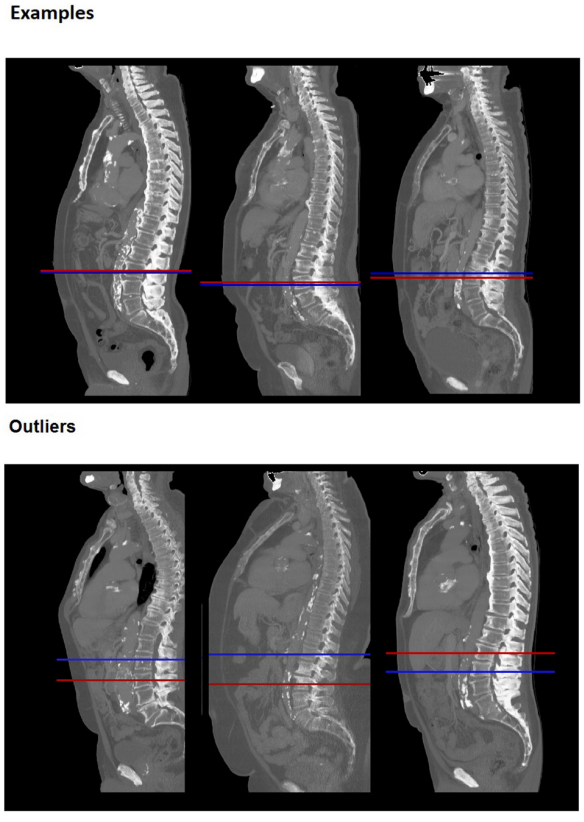

FIGURE 2 | Examples of slice selection. Upper random examples and lower largest outliers, for 6 different patients. Red line: manually selected slice, Blue line: automatically selected slice. The bottom left and bottom middle example were incorrectly selected in the automatic analysis, which identified slices at L2 and L1 level, respectively. The bottom right example was incorrectly selected by the manual method and is correctly identified by the automatic analysis.

TABLE 2 | Comparison between manual and automatic segmentation, slice selection and fully automatic assessment of psoas muscle area.

Full automatic	**Manual PMA cm^2**	**Automatic PMA cm^2**	**Bias [95% Limit of agreement], cm^2**	**ICC [95%CI]**	**CV [95%CI]**	
Psoas muscle area	15.4 ± 4.6	14.7 ± 4.7	−0.69 [−6.60−5.23]	0.78 [0.74−0.82]	11.2% [10.2−12.2]	
Gender						
Male	18.6 ± 4.3	18.1 ± 4.1	−0.47 [−7.25–6.31]	0.66 [0.59–0.73]	10.0% [8.6–11.4][a]	
Female	12.8 ± 2.9	11.9 ± 3.0	−0.86 [−5.93–4.21]	0.59 [0.49–0.68]	12.2% [10.8–13.6][a]	
BMI groups						
Normal/underweight	14.9 ± 4.2	14.6 ± 4.3	−0.39 [−6.14–5.36]	0.77 [0.70–0.82]	11.5% [9.6–13.4]	
Overweight	15.6 ± 4.8	14.9 ± 4.7	−0.70 [−6.50–5.09]	0.80 [0.74–0.85]	10.2% [9.0–11.4]	
Obese	15.7 ± 4.7	14.7 ± 5.1	−1.05 [−7.32–5.23]	0.77 [0.68–0.84]	12.5% [10.6–14.4]	
Slice selection only	**Manual slice selection, mm**	**Automatic Slice selection, mm**	**Bias [95% Limit of agreement], cm^2**	**ICC [95%CI]**	**CV [95%CI]**	
Slice selection L3	253 ± 28	256 ± 28	3.4 [−24.5–31.4]	0.86 [0.83–0.89]	3.0% [2.8–3.3]	
Gender						
Male	261 ± 26	263 ± 28	1.9 [−25.3–29.1]	0.87 [0.83–0.89]	2.7% [2.4–3.0][a]	
Female	246 ± 27	251 ± 28	4.7 [−23.7–33.1]	0.85 [0.80–0.89]	3.3% [2.9–3.7][a]	
BMI groups						
Normal/underweight	254 ± 27	253 ± 27	−0.9 [−29.0–27.2]	0.86 [0.82–0.89]	3.0% [2.6–3.4]	
Overweight	253 ± 29	257 ± 29	4.7 [−21.1–30.4]	0.89 [0.84–0.92]	3.0% [2.5–3.2]	
Obese	252 ± 26	259 ± 28	7.0 [−21.9–35.9]	0.83 [0.71–0.89]	3.4% [3.0–3.7]	
Segmentation only	**Manual PMA, cm^2**	**Automatic PMA, cm^2**	**Bias [95% Limit of agreement], cm^2**	**ICC [95%CI]**	**CV [95%CI]**	**Dice Index Mean ± SD**
Psoas muscle area	15.4 ± 4.6	14.9 ± 4.6	−0.55 [−2.80–1.71]	0.96 [0.93–0.98]	4.4% [4.0–4.8]	0.93 ± 0.04
Gender						
Male	18.6 ± 4.3	18.1 ± 4.2	−0.48 [−3.02–2.07]	0.95 [0.92–0.96]	s3.7% [3.3–4.1][a]	0.94 ± 0.03[a]
Female	12.8 ± 2.9	13.1 ± 3.0	−0.61 [−2.59–1.38]	0.92 [0.82–0.96]	5.0% [4.4–5.6][a]	0.92 ± 0.05[a]
BMI groups						
Normal/underweight	14.9 ± 4.2	14.2 ± 4.2	−0.36 [−2.13–1.41]	0.94 [0.85–0.97]	5.2% [4.3–6.0]	0.92 ± 0.06
Overweight	15.6 ± 4.8	15.1 ± 4.8	−0.49 [−2.85–1.88]	0.96 [0.94–0.98]	4.3% [3.7–4.8]	0.94 ± 0.03[b]
Obese	15.7 ± 4.7	15.3 ± 4.8	−0.36 [−2.13–1.41]	0.98 [0.97–0.99]	3.6% [3.1–4.1] [b]	0.94 ± 0.03[b]

[a]CV significant different from other gender; [b]significant different from normal/underweight BMI; ICC, intraclass correlation coefficient; CV, coefficient of variation; SD, standard deviation; C, confidence interval.

to 31.4 mm. Visual inspection showed that 84% of the slices were on the same vertebra in both methods. The other 16% of the automatic selected slices were one slice higher or lower than the manual selected slice and one scan had an automatic selected slice two vertebra higher than the manual selected slice (**Figure 2**). Slice selection had an ICC of 0.86 [95% CI: 0.83–0.89] and a within-subject CV of 3.0% [95% CI: 2.8–3.3]. For slice selection male patients had a significantly lower within-subject CV than female patients, 2.7% [2.4–3.0] vs. 3.3% [2.9–3.7] ($p = 0.01$). There were no significant differences between BMI groups.

Evaluation of Psoas Muscle Segmentation on the Manual Selected Slice

Average psoas muscle area was 15.4 ± 4.6 cm^2 for manual segmentation and 14.9 ± 4.6 cm^2 for the automatic segmentation (**Table 2**). Median difference between methods was 0.69 cm^2 [IQR:0.31–1.19], and Bland-Altman analysis (**Figure 1**) showed a bias of −0.55 cm^2 with a 95% limit of agreement of −2.80 to 1.71 cm^2 and an ICC of 0.96 [95% CI: 0.93–0.98]. Overall Dice index was 0.93 ± 0.04 and within-subject CV was 4.4% [95% CI: 4.0–4.8]. Examples of three randomly segmented CT scans and the three largest outliers, based on within-subject CV are shown in **Figure 3**. For male patients the Dice index was significantly higher 0.94 ± 0.03 vs. 0.92 ± 0.05 ($p < 0.001$) and the within-subject CV was significantly lower 3.7% [3.3–4.1] vs. 5.0% [4.4–5.6] ($p < 0.001$) than for female patients. Overweight and obese patients had significantly higher Dice index than patients in the normal/underweight group, 0.94 ± 0.03 and 0.94 ± 0.03 vs. 0.92 ± 0.06 ($p < 0.001$), respectively. The within-subject CV was significant lower in obese patients compared to the normal/underweight group, 3.6% [3.1–4.1] vs. 5.2% [4.3–6.0] ($p = 0.008$).

DISCUSSION

The aim of the study was to compare fully automatic psoas muscle area measurements and manual psoas muscle area measurements on a CT scan at the level of L3 vertebra. The results showed that automatic slice selection identified slices on the same vertebra as the manual selection in 84% of the cases and otherwise

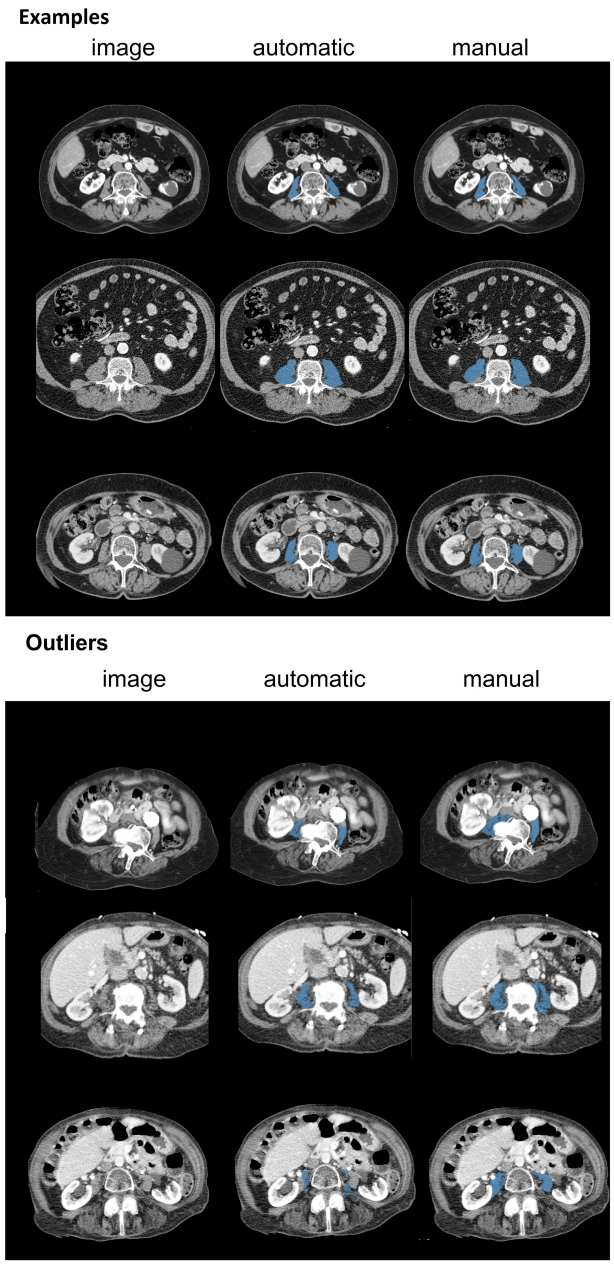

FIGURE 3 | Examples of three randomly selected CT scans and three largest outliers for 6 different patients. Dice indices for these examples were 0.92 (top row), 0.90 (middle row) and 0.93 (bottom row). Dice indices for outliers were 0.74 (top row), 0.75 (middle row) and 0.36 (bottom row). The outlier shown in the top row contains an artifact, the middle row shows an overexposed vertebra and the bottom row shows an uncommon distribution of connective tissue, organs and muscle area and is incorrectly segmented by the automatic software.

was one vertebra higher of lower than manual selected slice. The Dice index for the psoas segmentation was high with a score of 0.93, which means that overlap between methods is on average 93%.

This is the first study to evaluate assessment of the psoas muscle at L3 level in CT scans with automatic deep learning-based software (12). Concurrent slice selection between the manual and automatic method was correct in a vast majority off the CT scans. The median difference was 7.5 mm which is well within the range of the L3 vertebra, with a height of approximately 30 mm (20). Given that there is no substantial change of psoas muscle area over the entire vertebra height at the L3 level (8), it can be expected that small variations in slice selection within the range of L3 vertebra do not lead to a systematic segmentation error (21, 22). Besides a good performance on slice selection, we also observed that the difference between the manual and automatic segmentation is comparable with the interobserver variability of the manual method performed by trained researchers (16, 23, 24). Indeed, multiple studies in TAVR and pancreatitis patients observed an interobserver ICC of approximately 0.97 between trained researchers, which is close to our observed ICC of 0.96 (16, 23, 24).

In-depth analysis showed differences in Dice index and within-subject CV between the manual and automatic method for sex and BMI. Male, overweight and obese patients had a higher Dice index and lower within-subject CV compared to the female and normal/underweight patients. These results could be explained by the larger psoas muscle area in the male and overweight patients. Incorrectly segmented voxels in one of the methods have relatively less impact in patients with a larger psoas muscle area. Furthermore, these patients have relatively less transition from the psoas to the quadratus lumborum and erector spinae, because this area is more prone to segmentation errors, less transition area leads to lower differences (8). Similar results have been found earlier in other studies, in which groups with larger psoas muscle area also showed a higher Dice index between methods (13). However, differences were only small and most likely not clinically significant.

The results of this study have important implications for research and clinical practice. Automatic software provides the possibility to process large sets of CT scans without high costs of time and expertise. Large scale studies can be performed on available routine clinical scans in various patient populations to search for imaging biomarkers that predict clinical outcomes such as total muscle area at the level of L3 vertebra, muscle quality which can be measured as muscle density, or intra- and intermuscular adipose tissue (25). Furthermore, segmentation of muscle mass and muscle quality can easily be performed over multiple slices. Future research can therefore focus on muscle volume instead of muscle area. Some studies with deep learning have already been performed correctly determining volume of iliopsoas (26). However, it is currently unknown if complete volume is also predictive of clinical outcomes. Therefore, our study first focused on complete manual slice selection and segmentation of psoas muscle area on single slice. For clinical practice the fully automatic method can offer tremendous opportunity, as it could be applied, with limited overhead, alongside any clinical protocol that includes abdominal CT. The automatic method makes it possible to use this data during daily clinical practice. The information about muscle mass

can be used to identify frail, malnourished or sarcopenic patients at higher risk of adverse clinical outcomes, which is currently not used in clinical practice (1, 2). In TAVR patients, other surgical patients and community based older adults it is already shown that low muscle mass and low psoas muscle area are associated with negative clinical outcomes including length of stay, physical decline and mortality (3, 27, 28). Patients identified with low muscle mass can be selected to receive extra specialized care and preventive treatment including supervision from a dietician and physiotherapist to increase muscle mass, which is of interest for future research (29, 30).

This is the first study that applies deep learning-based software for automatic muscle assessment on the CT scan in a large cohort of elderly cardiac patients. In-depth analysis of the method comprised of slice selection and segmentation was performed providing a complete overview of the performance of the automatic muscle assessment. The study has some limitations. First, the comparison between automatic and manual segmentation was limited to psoas muscle area, while the software can also segment abdominal muscle area, long-spine muscle area, visceral fat area and subcutaneous fat area. However, the narrow field of view of the scans prohibited accurate analysis of these tissues in several patients. Second, the study is single center by design and includes only patients planned for TAVR, i.e., patients with severe aortic stenosis. However, the employed body composition method is trained using images from various patient populations and with various acquisition protocols (e.g., with and without contrast agents). It is likely that the performance of the method will generalize to other cohorts, because muscle composition is relatively similar among cohorts (31–33). However, this hypothesis should be confirmed in future studies, especially in groups with extreme or deviating muscle composition. Finally, manual segmentation and slice selection were used as reference standard. Although manual segmentation is generally an accepted method, which is validated and has good performances, manual slice selection and segmentation can contain human errors, as can be seen by the largest outliers in this study.

To conclude, fully automatic deep learning-based assessment of muscle area on a CT scan offers an accurate and reliable alternative for the currently used manual method. It is a tool that offers great opportunities for analysis in large scale studies and in clinical applications.

DATA AVAILABILITY STATEMENT

The dataset used in this study can be found in an online repository with digital object identifier: doi: 10.21942/uva.19403444.v1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the METC AMC. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DV, RD, and JS performed the first draft of the manuscript in close cooperation with all other authors. MV and YJ performed manual slice selection and segmentation. PM performed the automatic deep learning assessment of the psoas muscle area, both blinded for the contradicting method. DV performed the performance of all analysis. All authors did cooperate in the concept and design of the manuscript, interpretation of data and gave critical revision on the full manuscript.

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Conflict of Interest: PM was employed by Quantib-U. BD was Artificial Intelligence lead and cofounder of Quantib-U. II was a cofounder and Scientific lead at Quantib-U.

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The Use of Bioelectrical Impedance Analysis Measures for Predicting Clinical Outcomes in Critically Ill Children

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Background: The study aimed to investigate the association of bioelectrical impedance analysis (BIA) for predicting clinical outcomes in critically ill children.

Methods: This single-center prospective observational study included patients admitted to a mixed Pediatric Intensive Care Unit (PICU). All patients underwent anthropometric measurement and BIA measurements in the first 24 h of admission. The patients were classified into different groups based on body mass index (BMI) for age. Electronic hospital medical records were reviewed to collect clinical data for each patient. All the obtained data were analyzed by the statistical methods.

Results: There were 231 patients enrolled in our study, of which 31.6% were diagnosed with malnutrition. The phase angle (PhA) of 90-day survivors was significantly higher than that of the non-survivors (4.3° ± 1.1°vs. 3.1° ± 0.9°, $P = 0.02$). The age-adjusted Spearman partial correlation analysis showed a weak negative correlation between PhA and duration of medical ventilation ($r_S = -0.42$, $P < 0.05$). Furthermore, length of stay in PICU has a very weak correlation with ECW/TBW ($r_S = 0.29$, $P < 0.05$), and a negative correlation with protein ($r_S = -0.27$, $P < 0.05$). Multivariate analysis found that PhA was a significant predictor associated with the 90-day mortality when it was adjusted for PRISM III score (adjusted OR = 1.51, CI: 1.10–2.07, $p = 0.01$). The area under the ROC (AUROC) of PhA for predicting 90-day mortality was 0.69 (95% CI: 0.53–0.85, $p < 0.05$), and the cutoff value of PhA was 3.0°, with a sensitivity and specificity of 83 and 53%, respectively.

Conclusion: BIA-derived PhA was found to be an independent predictor of 90-day mortality among critically ill children. A low PhA was associated with a prolonged duration of medical ventilation.

Keywords: phase angle, critical illness, children, bioimpedance analysis, progonosis

INTRODUCTION

Malnutrition is highly prevalent in critically ill childrenin the pediatric intensive care unit (PICU) (1). Critically ill children usually experience total body water redistribution, edema, systemic metabolic status changes, and rapid lean body mass loss, thereby leading to their body composition changes dramatically and nutritional status deterioration. Worse nutritional status is often associated with unfavorable clinical consequences such as prolonged duration of mechanical ventilation, longer ICU (intensive care unit) length of stay, extended hospitalization length, and increased hospital mortality (2). However, the most used methods to assess the nutritional state including weight loss, body mass index (BMI), and biochemical indicators do not accurately reflect the real alteration of the nutritional status among critically ill children.

Bioelectrical impedance analysis (BIA) is a method of assessing body composition and its use in ICU patients has progressively increased (3). BIA measures impedance by applying a current through the body. The impedance consists of two components: resistance (R) and reactance (Xc). Human tissues have different contents of fluid and conducting electrolytes, thus the resistance of tissues is different. Human cell membranes and tissue interfaces can affect capacitive reactance. Therefore, body composition can be estimated by using BIA. Several studies have confirmed that BIA was a useful tool for assessing body composition and has a good relative agreement with dual-energy X-ray absorptiometry (DXA) in children (4, 5). Moreover, BIA is a portable, easy-to-use, non-invasive, and low-cost method. For this reason, coupled with children's comfort and cooperation, BIA is significantly appropriate for children in daily clinical practice.

Recently, some studies have pointed out that BIA can be served as a good predictor to evaluate the disease severity among critically ill adults (6), especially BIA-derived phase angle (PhA). PhA was calculated using the following equation: $PhA = (Xc/R) \times (180/\pi)$. It can reflect the integrity of the cellular membrane, total body cell mass, and hydration status of the body (4, 5). Lower PhA always represent the poorer the prognosis. A systematic review found PhA seemed to be a good indicator of mortality in many clinical situations (7). However, studies on assessing the association between BIA measurements parameters and clinical outcomes in PICU patients are lacking.

This present study aimed to determine whether BIA measurements parameters on PICU admission independently predicts adverse clinical outcomes among critically ill children.

Abbreviations: AMC, Arm muscle circumference; BIA, Bioelectrical impedance analysis; BF, Body fat; BMI, Body mass index; BCM, Body cell mass; BMC, Bone mineral content; ECW, Extracellular water; FM, Fat mass; BF, body fat; FM, Fat mass; FFM, Fat-free mass; ICW, Intracellular water; LOS, Length of stay; MV, Mechanical ventilation; PICU, Pediatric intensive care unit; PhA, Phase angle; PICS, Pediatric Critical Illness Score; PRISM, Pediatric Risk of Mortality; SMM, Skeletal muscle mass; TLC, Total lymphocyte count; TBW, Total body water; TBW/FFM, Total body water/fat free mass; WHO, World Health Organization.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective observational single-center study at the PICU of a tertiary hospital from March 2019 to November 2021. Our PICU is a mixed ICU that receives medical and surgical patients. This study was approved by the Chengdu Women's and Children's Central Hospital in Sichuan, China [Registration No. 2019(11)].

Inclusion criteria were patients admitted to the PICU with an age range of 1–18 years. The exclusion criteria were as follows: (1) patients with any amputation, or with skin injury on the area where the electrodes of the BIA instrument would be placed, (2) underwent dialysis 2 h before BIA, (3) with congenital chromosomal abnormalities or hereditary metabolic diseases, (4) with serious errors in their BIA results. Written informed consent was obtained from parents and/or legal guardians.

Anthropometric Measurement and Classification of Nutritional Status

Anthropometric measurement was performed in the first 24 h of admission. To reduce the possibility of errors, all measurements were performed by a trained PICU physician. Weight was measured using a scale that was calibrated for accuracy before each use. Infants were weighed using a scale accurate to 5 g. Children who could not be weighed standing were held by an adult. The child's weight was obtained by subtracting the weight of the adult from the total weight of the child and adult. Children aged 3 years or younger assumed the supine position for the measurement. Length was measured using a pediatric anthropometer with an accuracy of 0.1 cm. In children aged older than 3 years, height was measured using a stadimeter with an accuracy of 0.1 cm. In children whose condition prevented the use of conventional measuring techniques (e.g., patients who were mechanically ventilated or taking vasoactive drugs and above 1 m), the ulna length was measured using a pediatric anthropometer. Height and length prediction was extrapolated by Gauld et al. (8). Arm muscle circumference (AMC) was measured using a metric tape marked in 0.5-cm increments. Measurements were taken at the midpoint of the distance between the acromion and olecranon with the arm extended along the body.

BMI was calculated using the following equation: BMI/A = W (kg)/H^2 (m). Nutritional status was classified based on BMI for age using the World Health Organization (WHO) growth charts as the reference. Patients were categorized as the non-malnourished group, moderately malnourished group, and severely malnourished group, defined by weight for age 0 to −2 standard deviation (SD),−2 to −3 *SD*, and less than −3 *SD* of the WHO growth charts, respectively.

Demographic, Clinical, and Biochemical Data

Hospital electronic medical records (EMR) were reviewed to collect data for each patient, including age, diagnosis, height,

weight, length of hospital stay, length of PICU stay, duration of mechanical ventilation (MV), and other notable characteristics. Hospital Mortality was defined as death during PICU stay. The patients who died at 90 days after PICU admission were ascertained by hospital EMR review, telephone contact, and clinical follow-up data. Blood was collected within 24 h after admission. Blood biochemical indexes, such as serum albumin level, total lymphocyte count (TLC), and hemoglobin level were also collected from EMR. Pediatric Risk of Mortality (PRISM) score which is based on 14 routinely measured, physiologic variables, and 23 variable ranges, was collected at the time of admission as a prognostic indicator, and judging severity of the disease.

Bioelectrical Impedance Analysis Data

InBodyS10 (Biospace, Seoul, South Korea) was used for the measurements of the study. The device uses an alternating current of 220 volts with a frequency of 50 kHz. Patients were immobilized in a supine position with their arms were separated from the trunk and feet comfortably apart. Subsequently, surface electrodes were placed on the patient's thumbs and middle fingers and two sides of the ankles, after disinfection with 70% alcohol. The results of the resistance (R) and reactance (Xc) were obtained after sending a weak electric current through the body. BIA measurements were directly displayed on the device, including intracellular water, extracellular water (ECW) and total body water (TBW), ECM/TBW, body cell mass, bone mineral content, skeletal muscle mass, FM (fat mass), % body fat (%BF), TBW/FFM (fat-free mass), proteins, and minerals. All participants underwent BIA within 24 h after admission.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 (IBM Corp, Armonk, NY, United States). Normalities of data distributions were confirmed using the Kolmogorov—Smirnov test. Normally distributed quantitative data are presented as the mean ± standard deviation (Mean ± *SD*). Categorical variables were presented as frequencies and proportions. Abnormally distributed continuous variables are presented as the median (25th and 75th percentiles). Continuous variables were compared and analyzed based on the independent sample *t*-test and analysis of variance. Qualitative data were compared by X^2 test. Age-adjusted Spearman partial correlation analysis was performed to explore the correlation between the BIA measurements and duration of MV, length of ICU stay, and length of hospital. Univariate and multivariable logistic regression analyses were performed to determine the predictive factors of 90-day mortality. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curves were established to evaluate the predictive abilities value of phase angle. The area under the ROC curve (AUC) and its 95% confidence interval (CI) were measured. The optimal cutoff values for ROC curves were established using the Youden index. *P*-value < 0.05 was considered statistically significant.

RESULTS

A total of 231 patients were included during the study period. All patients were divided into three groups according to their BMI. Among them, 158 were non-malnourished, 34 were moderately malnourished, and 39 were severely malnourished. There were significant differences in ages, duration of mechanical ventilation, and 90-day mortality among the three groups ($P < 0.05$). In the severely malnourished group, the longest duration of MV and the highest mortality were seen. No statistically significant difference was found in length or height, weight, PRISM III score, the percentage of invasive mechanical ventilation, mortality in PICU, length of stay in PICU, and length of stay in hospital in different nutritional status groups. The comparison of general characteristics and clinical outcomes of patients is described in **Table 1**.

Table 2 provides a comparison of the nutritional indicators and BIA measurements between 90-day survivors and non-survivors. The results showed that the BMI, albumin levels, and PhA were significantly different between the two groups ($P < 0.05$). The PhA of 90-day survivors was significantly higher than that of the non-survivors ($4.3° \pm 1.1°$vs. $3.1° \pm 0.9°$, $P = 0.02$). No statistical difference was observed in weight, AMC, TLC, hemoglobin, and the remaining BIA measurements.

Due to the significant differences in child's age among the three nutrition status groups, we used the age-adjusted Spearman partial correlation analysis to explore the association between the BIA measurements and different clinical outcomes (**Table 3**). There was a weak negative correlation between PhA and the duration of medical ventilation ($r_s = -0.42$, $P < 0.05$). Furthermore, length of stay in PICU has a weak correlation with ECW/TBW ($r_s = 0.29$, $P < 0.05$), and a weak negative correlation with protein ($r_s = -0.27$, $P < 0.05$).

Variables with statistically significant differences ($p < 0.05$) between 90-day survivors and non-survivors groups were tested in univariate and multivariate logistic analysis with adjustment confounding factors (age and PRISM III score). Univariate logistic regression analysis showed that PhA (as a continuous variable) and PRISM III score were associated with 90-day mortality (PhA: odds ratio (OR) = 1.54, confidence interval (CI): 1.09–2.17, $p = 0.01$; PRISM III score: OR = 0.89, CI: 0.82–0.98, $p = 0.04$). BMI, albumin, and age were not associated with 90-day mortality, nor were they confounders for the effect of PhA on 90-day mortality. Multivariate analysis suggested that PhA was a significant predictor associated with the 90-day mortality when PhA was adjusted for PRISM III score (adjusted OR = 1.51, CI: 1.10–2.07, $p = 0.01$ PRISM III score also was an independent predictor (OR = 0.89, CI: 0.83–0.98, $p = 0.01$) (see **Table 4**). No significant differences were found for BMI and albumin.

The results of the Receiver Operating Characteristic (ROC) curve analysis are provided in **Figure 1**. The area under the ROC (AUROC) of PhA was 0.69 (95% CI: 0.53–0.85, $p < 0.05$), and the cutoff value of PhA was 3.0°, with a sensitivity and specificity of 83 and 53%, respectively.

TABLE 1 | Comparison of general characteristics, clinical outcomes among the different nutrition status groups (n = 231).

Variables	Non- malnourished (n = 158)	Moderately malnourish (n = 34)	Severely malnourished (n = 39)	P-value
Age (years)	1.90 (1.10–4.38)	2.40 (1.53–5.30)	4.90 (1.70–10.00)	0.03*
Male sex (%)	73.50%	71.40%	63.20%	0.68
Length or height (cm)	87.50 (78.00–107.00)	94.50 (78.25–114.25)	115.00 (82.00–132.00)	0.14
Weight (Kg)	12.50 (10.30–16.00)	11.25 (8.88–16.50)	14.00 (8.50–22.50)	0.58
PRISM III score	8.48 ± 3.94	10.32 ± 4.64	11.69 ± 3.71	0.48
MV, *n* (%)	56 (35.4)	10 (29.4)	19 (48.7)	0.50
Duration of MV, days	5.00 (3.00–7.00)	5.00 (4.00–14.00)	11.50 (6.00–16.00)	0.02*
PICU mortality, *n* (%)	5 (2.16%)	2 (0.086%)	4 (1.73%)	0.48
90-day mortality	6 (2.59%)	3 (1.30%)	15 (6.4%)	0.02*
LOS in PICU, days	7.00 (6.00–10.00)	8.00 (3.00–11.75)	11.20 (2.75–15.00)	0.86
LOS in hospital, days	13.00 (9.00–27.75)	14.00 (10.50–22.00)	14.00 (10.00–22.00)	0.89

*$P < 0.05$.

Quantitative data was shown as ($\bar{x}$ ± SD) or median (25th and 75th percentiles). Qualitative data was showed as numbers (percentage). PRISM, pediatric risk of mortality; LOS, length of stay; MV, mechanical ventilation; PICU, pediatric intensive care unit.

TABLE 2 | Comparison of the nutritional indicators and BIA measurements between 90-day survivors and non-survivors.

Variables	Survivors(n = 158)	Non-Survivors(n = 34)	P-value
Weight (Kg)	14.5 (10.0–16.0)	16.4 (12.1–21.5)	0.41
BMI, kg/m^2	15.6 ± 2.4	13.9 ± 3.2	0.03*
AMC, cm	15.0 ± 1.3	15.5 ± 1.9	0.16
Albumin, g/dL	38.7 ± 6.3	37.2 ± 9.0	0.03*
TLC, cell/mm^3	2.4 (1.3–3.1)	2.2 (0.9–4.3)	0.39
Hemoglobin, g/dL	109.8 (99.0–122.0)	120.5 (92.0–127.5)	0.24
PhA	4.3 ± 1.1	3.1 ± 0.9	0.02*
BCM, kg	7.6 (4.8–9.7)	8.3 (5.3–9.6)	0.81
BMC, kg	0.7 (0.3–1.0)	0.7 (0.5–1.0)	0.22
SMM, kg	4.9 (2.4–6.8)	5.4 (2.8–6.7)	0.74
FM, kg	2.2 (1.6–3.8)	2.3 (0.6–2.8)	0.45
%BF	18.3 (7.4–27.6)	17.7 (3.0–22.5)	0.87
Protein, kg	2.3 (1.5–2.9)	2.5 (1.6–2.9)	0.64
Mineral, kg	0.8 (0.4–1.2)	0.9 (0.6–1.1)	0.27
ICW	5.3 (3.4–6.8)	5.8 (3.7–6.7)	0.65
ECW	3.6 (2.4–4.3)	4.07 (2.62–4.37)	0.601
TBW	8.9 (5.67–11.1)	9.9 (6.3–11.9)	0.44
ECW/TBW	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.27
%TBW/FFM	74.7 ± 1.6	74.4 ± 1.5	0.55

*$P < 0.05$.

Values shown are mean ± SD (standard deviation), number (percentage) or median [IQR]. BMI, body mass index; AMC, arm muscle circumference; TLC, total lymphocyte count; BCM, Body cell mass; BMC, bone mineral content; SMM, skeletal muscle mass; FM, fat mass; BF, body fat; ICW, intracellular water; ECW, extracellular water; TBW, total body water; TBW/FFM, total body water/fat free mass.

TABLE 3 | Spearman's correlation coefficients between BIA measurements and clinical outcomes among all admitted patients.

Variables	Duration of MV	LOS in PICU	LOS in hospital
PhA	−0.42*	−0.14	−0.15
BCM, kg	−0.03	−0.05	0.08
SMM	−0.01	−0.12	0.14
FM	0.07	−0.11	0.10
%BF	0.15	−0.05	−0.05
Protein, kg	−0.07	−0.27*	0.14
Mineral, kg	−0.02	−0.07	0.19
ICW	−0.13	−0.17	0.13
ECW	−0.15	0.15	0.17
TBW	−0.14	0.19	0.15
ECW/TBW	0.04	0.29*	0.14

*$P < 0.05$.

BCM, body cell mass; BMC, bone mineral content; SMM, skeletal muscle mass; FM, fat mass; BF, Body fat; ICW, intracellular water; ECW, extracellular water; TBW, total body water; TBW/FFM, total body water/fat free mass; MV, medical ventilation; LOS, length of stay; PICU, pediatric intensive care unit.

DISCUSSION

The development of both convenient and accurate methods for assessing the mortality or adverse clinical outcomes of PICU patients has been urgently needed, especially among children. Early identification and proper assessment of nutritional status are crucial to improve the patients' outcomes (9–11). Bioelectrical impedance analysis (BIA) is a simple non-invasive assessment tool for body composition and therefore nutritional status. Beyond these, BIA is a rapid, low-cost, non-invasive, easy-to-perform, repeatable, and bedside feasible technique, it may be an alternative tool to death risk predictive scoring system to assess the severity of illness and predict the risk of mortality. This prospective observational study used BIA measurement parameters to assess the adverse clinical outcome of diseases in critically ill children. The result shows that the BIA-derived phase angle at PICU admission is an independent predictor of 90-day mortality. Children with PhA below 3° had 1.51 times higher adjusted risk of dying. A lower PhA was associated with a longer duration of mechanical ventilation (r_s = –0.42). Other BIA measurement parameters such as ECW/TBW and protein, had a very weak correlation with length of stay in PICU.

TABLE 4 | Logistic regression multivariate analysis of determinants of 90-mortality.

Variable	Univariable		Multivariable	
	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Phase angle (°)	1.54 (1.09, 2.17)	0.01*	1.51 (1.10, 2.07)	0.01*
PRISM III score	0.89 (0.82, 0.98)	0.04*	0.89 (0.83, 0.98)	0.01*
Age	1.12 (0.95, 1.31)	0.97		
BMI	0.98 (0.75, 1.26)	0.91		
Alb	0.97 (0.89, 1.06)	0.48		

**P < 0.05. PRISM: pediatric risk of mortality, BMI, body mass index; Alb, albumin. Age, gender, BMI, and PRISM III score-predicted mortality were tested for confounding.*

Age, gender, and BMI were no confounders. PRISM III score predicted mortality was a confounder and was adjusted for in the multivariable logistic regression analysis.

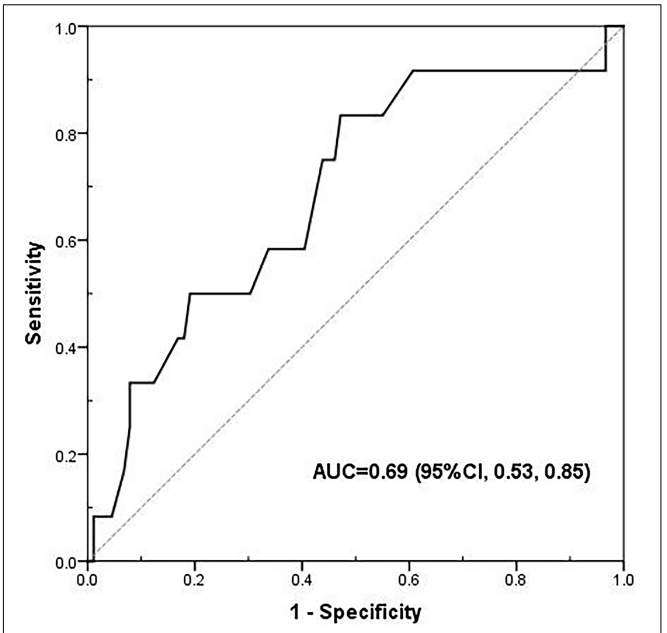

FIGURE 1 | The receiver operating characteristic (ROC) curve of phase angle for 90-day mortality. The area under the ROC (AUROC) was 0. 69 (95% CI: 0.53–0.85, $p < 0.05$), and the cut-off value of phase angle was 3.00°, with a sensitivity and specificity of 83 and 53%, respectively.

Malnutrition is common in critically ill children, with the prevalence rate of 31.6% (73/231) in our study. In contrast to adults, children are at a higher risk of experiencing malnutrition due to less nutritional stores and more nutrient consumption. Moreover, depleted muscle mass is associated with infectious complications, prolonged duration of MV, longer hospitalization, greater need for rehabilitation care after hospital discharge, and higher mortality (12). As this study showed, the patients in the malnourished group had a longer duration of MV and increased 90-day mortality than the normal nutritional status group ($P < 0.05$). Traditional anthropometric measurements might not accurately reflect body composition changes in life-threatening disease states. It is currently not possible to distinguish between overall weight loss or decreased BMI, this depletion comes from adipose tissue or muscle tissue. The multivariate regression analysis did not show an association between BMI and 90-day mortality, but rather between PhA and mortality in our study. Some studies showed that BIA measurements are better than anthropometry and blood biochemical analysis in the nutritional assessment of patients (4, 13–15). These findings emphasize the importance of body composition analysis to anthropometry in the ability of the nutrition assessment and predicting clinical outcomes.

BIA has unique advantages in this respect. Studies and systematic literature reviews (16, 17) have confirmed that BIA is a useful and reliable tool in the assessment of body composition in children and showed high specificity at detecting low muscle mass in patients. A recent study by Looijaard et al. (18) found that BIA-identified low skeletal muscle mass was consistent with CT scan, a golden standard method. Significant correlations have been detected for different BIA-derived muscle mass equations and CT-derived measurements (correlations ranging between 0.64 and 0.834). However, BIA also has some limitations. BIA measurements may have underestimated the presence of low muscle mass due to abnormal fluid redistribution in critically ill patients (19). Among younger infants (especially those aged less than 6 months), BIA may provide little benefit over anthropometry-based prediction equations. According to the result of previous studies, ECW/TBW ratios are useful and convenient tools used to assess the volume status of patients. the cut-off value for the assessment of edema was about 0.39 in adults (20–23). In our study, we measured the ECW/TBW ratio in all patients, and the median ECW/TBW ratio was greater than or equal to 0.40 in survivor and non-survivor groups. However, most of our patients did not display any edema symptoms. We hypothesize that children having higher water content than adults may be associated with a higher ECW/TCW ratio. There was a very weak association between length of stay in PICU and ECW/TCW ratio. It should be noted that BIA has intrinsic limitations in its ability to accurately distinguish between intravascular and interstitial volume in the extracellular compartment. Therefore, some recent studies have shown that bioelectrical impedance vector analysis, which visualizes impedance measurements (resistance and reactance), could be superior to any other parameter of the BIA for evaluating the hydration of critically ill patients in the ICU (24, 25).

BIA-derived PhA has been reported to be a good predictor of morbidity and mortality in different clinical situations (6, 26–28). PhA reflects the integrity of cell membranes and hydration status and is influenced by acute illness and general health. A low PhA always indicates cell membrane breakdown and decreased ability to store energy and complete metabolic functions. Considering the close correlation between PhA and nutrition status, it has been used to identify the patients at risk of nutrition status deterioration and worsening death. Stapel's (29) study found that

a PhA < 4.8° at ICU admission was an independent predictor of 90-day mortality in adults (adjusted odds ratio = 3.65, confidence interval: 1.34–9.93, $P = 0.011$). Zamberlan et al. (30). reported that among the BIA values, patients with PhA > 2.8°compared with patients with PhA ≤ 2.8° ($P < 0.0001$) showed a higher survival rate, and children with lower PhA values were more likely to remain in the PICU. Consistent with the result, we found that survivors showed significantly higher PhA compared with non-survivors. PhA < 3.0° at PICU admission was an independent predictor of 90-day mortality. In addition, we observed that lower PhA had a weak degree of correlation with the longer duration of MV. Other body composition parameters such as ECW, ICW, TBW, BCM, and skeletal muscle mass were not found to be an independent risk for death in our study. In our present study, significant differences in the levels of albumin and PRISM-III score were observed among the survivor group and the non-survivor group. Leite et al.'s (31) study showed that hypoalbuminemia at PICU admission is associated with higher 60-day mortality. However, we were not able to confirm the association between albumin and mortality. Several studies and meta-analyses (32–34) showed PRISM-III had good performance for mortality prediction in PICU. In our study, we confirmed that PRISM-III can be served as the indicator to an independently predictor of mortality.

Notably, PhA is affected by many factors, such as age, sex, level of physical activity, fluid status, and body composition (35). These factors contributed to the difficulty in analyzing the results among children. This is also the main limitation of the study. Furthermore, this was only a small single-center study and the results may not be generalizable. We still want to evaluate the clinical role of BIA measurements in critically ill children and establish appropriate PhA cut-points based on age, BMI, sex, and ethnicity in larger study populations.

CONCLUSION

This study found that BIA-derived PhA can be considered an independent predictor of 90-day mortality in critically ill children. The not high specificity of PhA suggests that clinicians should have a comprehensive evaluation of the PhA in conjunction with the patient's underlying disease status and other nutritional indicators, thereby contributing to clinical nutritional management and prognostic evaluation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Chengdu Women's and Children's Central Hospital, School of Medicine, UESTC. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

G-YZ: conception and design of the research. Z-HX and G-YZ: the acquisition of the data and the analysis of the data. Z-HX and X-MZ: writing—original draft. Z-HX, YQ, and M-JW: writing—review and editing. All authors contributed to the article and approved the submitted version.

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

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Efficacy of Glutamine in Treating Severe Acute Pancreatitis: A Systematic Review and Meta-Analysis

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Objectives: The prognosis of severe acute pancreatitis (SAP) patients is closely related to early nutritional support. It is well-established that changes in glutamine (Gln), an important amino acid and nutritional supplement, can reflect disease severity. However, no consensus has been reached on the role of Gln nutrition therapy for SAP patients. We conducted this systematic review and meta-analysis to summarize and evaluate the advantages of Gln supplementation in SAP.

Methods: PubMed, Web of Science, the Embase, Cochrane Library, and Chinese databases (CNKI, SinoMed, Wanfang, and VIP) were systematically searched for eligible studies that included glutamine supplementation in SAP patients from inception to October 31 2021, excluding non-SAP studies. Primary outcome measures included mortality, APACHE II score, complications, and length of hospital stay. The meta-analysis was registered with PROSPERO (CRD42021288371) and was conducted using Review Manager and Stata softwares.

Results: This meta-analysis included 30 randomized controlled trials (RCTs) with a total of 1,201 patients. Six primary outcomes and six secondary outcomes were analyzed. For the primary outcomes, Gln supplementation was associated with lower mortality (OR = 0.38, 95% CI: 0.21–0.69, $P = 0.001$), total hospital stay (MD = −3.41, 95% CI: −4.93 to −1.88, $P < 0.0001$) and complications (OR = 0.45, 95% CI: 0.31–0.66, $P < 0.0001$) compared with conventional nutrition. Further subgroup analysis found that parenteral glutamine was more effective in reducing mortality. In terms of secondary outcomes, Gln supplementation helped restore liver, kidney and immune function, with significantly increased serum albumin (SMD = 1.02, 95% CI: 0.74–1.31, $P < 0.00001$) and IgG levels (MD = 1.24, 95% CI: 0.82–1.67, $P < 0.00001$), and decreased serum creatinine (Scr) (MD = −12.60, 95% CI: −21.97 to −3.24, $P = 0.008$), and inflammatory indicators such as C-reaction protein (CRP) (SMD = −1.67, 95% CI: −2.43 to −0.90, $P < 0.0001$).

Conclusion: Although Gln supplementation is not routinely recommended, it is beneficial for SAP patients. Indeed, glutamine nutrition has little effect on some indicator outcomes but contributes to improving the prognosis of this patient population.

Systematic Review Registration: PROSPERO (york.ac.uk). Unique Identifier: CRD42021288371.

Keywords: glutamine, severe acute pancreatitis, treatment, prognosis, meta-analysis

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INTRODUCTION

Acute pancreatitis (AP) is a predominant cause of acute abdomen during clinical practice and can be divided into mild, moderately severe, and severe AP according to its severity (1). Although most cases present with mild disease, more than 20% of patients progress to severe acute pancreatitis (SAP) (2, 3). SAP is characterized by hemorrhagic and necrotizing pancreatitis that frequently causes systemic complications and multiorgan failure, resulting in high mortality and poor prognosis (4, 5). As an important feature of SAP, high metabolism and increased protein decomposition rate can easily lead to malnutrition and subsequent immunosuppression, further aggravating SAP (6, 7). Early fasting is a crucial part of the conservative treatment of AP to reduce the secretion of pancreatic enzymes and the inflammatory response. However, it should be borne in mind that due to the high metabolic activity of the disease itself and the lack of exogenous nutritional supplements, early fasting can lead to the further progression of SAP, which ultimately increases the hospitalization time, medical costs and mortality (8, 9). Mounting evidence suggests that early enteral or parenteral nutrition support can help reduce multisystem organ failure (MOF), pancreatic infection complications and mortality, leading to a better prognosis (10).

As the most abundant amino acid in the human body, glutamine (Gln) is widely utilized by the liver, lung and intestine, and its supplementation may correct the negative nitrogen balance caused by SAP, reduce inflammation and improve prognosis (11, 12). However, much controversy surrounds the use of Gln in the treatment of SAP. Petrov et al. (13) found that Gln-supplemented enteral nutrition did not reduce total infectious complications relative to standard enteral nutrition ($P = 0.53$). This standpoint was confirmed in a meta-analysis by Jiang et al. (14), who demonstrated that Gln-containing enteral nutrition could significantly reduce the risk of multiple organ dysfunction syndromes (MODS) and death and shorten the length of hospital stay. Another study found that parenteral nutrition supplemented with Gln was more effective than enteral nutrition in reducing complications such as infection, pseudocyst and necrosis, but the difference was not statistically significant (15). This is significantly inconsistent with the study by Li et al., who believed that enteral nutrition was more meaningful than parenteral nutrition in reducing pancreatic infection and related complications in patients (OR, 0.41; 95% CI, 0.22–0.77; $P = 0.006$) (16). In a randomized controlled study that enrolled patients with SAP ($n = 47$), Gln-containing parenteral nutrition significantly increased serum albumin levels, decreased mortality and morbidity, shortened hospital stay, and improved patient nutritional status (17). The conclusion was consistent with Tina et al. (18). They confirmed that parenteral Gln supplementation significantly reduced the risk of infectious complications by enrolling 226 AP patients (RR = 0.59; 95% CI, 0.39–0.88; $P \leq 0.05$) and mortality (RR = 0.26; 95% CI, 0.11–0.59; $P \leq 0.001$) and shorter length of hospital stay (MD = −2.93 days; 95% CI, −4.70 to −1.15; $P \leq 0.001$). However, the length of hospital stay was not consistent with Varsha et al. (MD = −1.35; 95% CI, −3.25 to 0.56, $P = 0.17$) (19). Therefore, much heterogeneity surrounds the application of Gln-containing nutritional support therapy in SAP. In addition, the 2019 Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis stated that the application of Gln preparations to SAP patients is beneficial to protect the intestinal mucosal barrier (20), but this was not mentioned in the American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis (21). Although a meta-analysis by Li et al. (22) attempted to evaluate the efficacy of Gln-rich nutritional support for SAP patients, the small number of included studies limited robustness of the findings. To this end, we included updated studies and data for meta-analysis, including 30 randomized controlled trials (RCTs) and a large sample of more than 1,800 patients. In addition, we performed subgroup analyses of Gln supplementation patterns and even detailed supplementation doses, which were not addressed in previous studies. This will provide more reliable and robust evidence for the efficacy of Gln-containing nutritional therapy.

TABLE 1 | Retrieval strategy of PubMed.

Number	Search strategy
#1	"Glutamine" [MeSH]
#2	"L-Glutamine" [Title/Abstract]
#3	"L Glutamine" [Title/Abstract]
#4	"D-Glutamine" [Title/Abstract]
#5	"D Glutamine" [Title/Abstract]
#6	"Gln" [Title/Abstract]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	"Pancreatitis, Acute Necrotizing" [MeSH]
#9	"Necrotizing Pancreatitis, Acute" [Title/Abstract]
#10	"Pancreatitis Necrotising" [Title/Abstract]
#11	"Acute Necrotizing Pancreatitis" [Title/Abstract]
#12	"Pancreatitis Necrotizing" [Title/Abstract]
#13	"Necrosis, Pancreatic" [Title/Abstract]
#14	"Hemorrhagic Necrotic Pancreatitis" [Title/Abstract]
#15	"Hemorrhagic Necrotic Pancreatitides" [Title/Abstract]
#16	"Necrotic Pancreatitis, Hemorrhagic" [Title/Abstract]
#17	"Pancreatitis, Hemorrhagic Necrotic" [Title/Abstract]
#18	"Severe Acute Pancreatitis" [Title/Abstract]
#19	"SAP" [Title/Abstract]
#20	#1 OR #2 OR #3 #8OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	#7 AND #20

METHODS

Our study was registered in the PROSPERO database (CRD42021288371). This study was conducted according

Abbreviations: SAP, severe acute pancreatitis; Gln, glutamine; RCTs, randomized controlled trials; Scr, serum creatinine; CRP, C-reaction protein; AP, acute pancreatitis; MOF, multisystem organ failure; MODS, multiple organ dysfunction syndromes; RR, relative risk; MD, mean difference; SMD, standard mean difference; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; BUN, blood urea nitrogen; IL-6, interleukin- 6; TNF-α, tumor necrosis factor α.

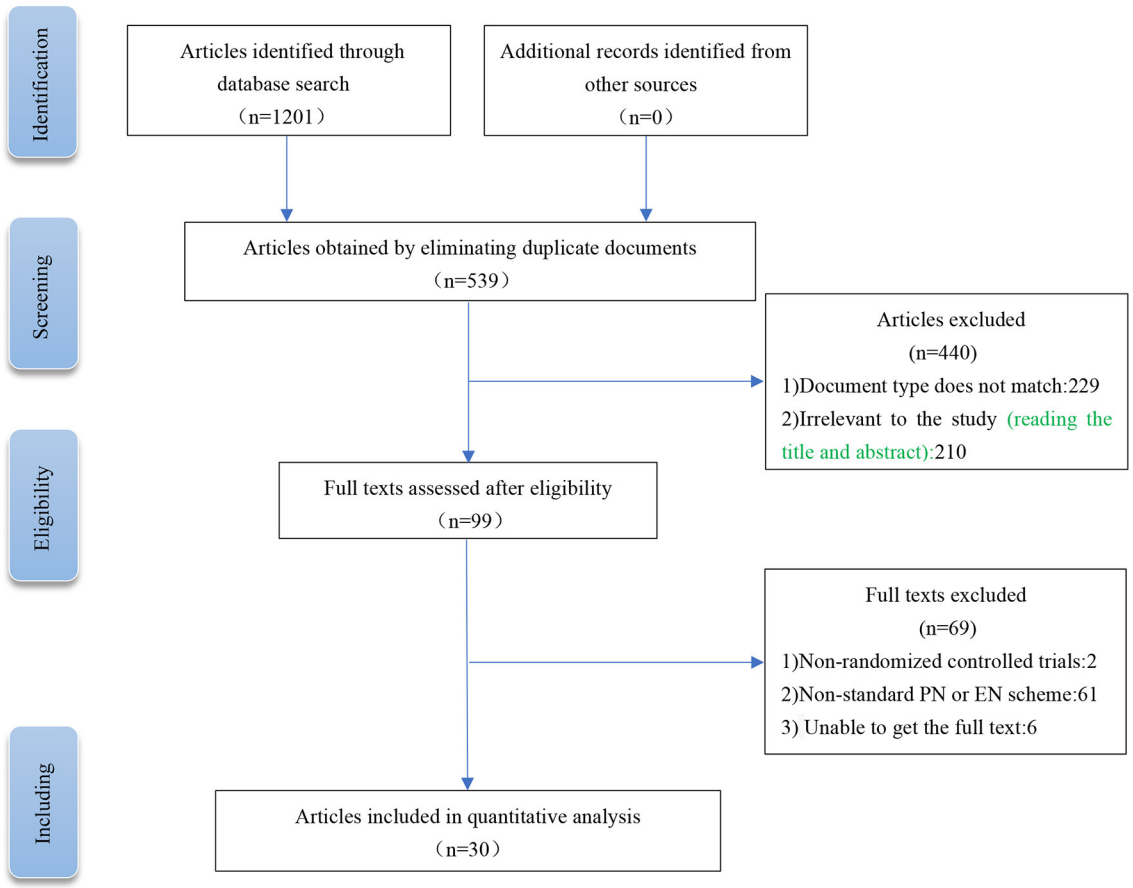

FIGURE 1 | Current meta-analysis article searching and screening strategies.

to the Cochrane Handbook 6.0, and the results were presented according to the PRISMA statement (23, 24).

Search Strategy

Databases, including PubMed, Web of Science, the Embase, Cochrane Library, and Chinese databases (CNKI, SinoMed, Wanfang, and VIP), were searched until October 31, 2021. We used the following subject headings plus free words: "SAP (or severe acute pancreatitis, or acute necrotizing pancreatitis, or hemorrhagic necrotic pancreatitis)" and "Gln (or glutamine, or L-Glutamine, or D-Glutamine);" other quality conference papers and journals were also searched. The specific retrieval strategy for PubMed database is provided in **Table 1**.

Inclusion and Exclusion Criteria

Study selection was based on the following criteria: (1) study population: SAP patients; (2) intervention and comparison: treatment with Gln (supplemented enterally or parenterally) or without Gln for SAP patients; (3) outcomes: primary outcomes such as mortality, APACHE II score, shortening intensive care unit (ICU) hospital stay, total length of hospital stay, bloating recovery time, complications and secondary outcomes such as liver function indicators [serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL)], kidney function indicators [serum creatinine (Scr) and blood urea nitrogen (BUN)], inflammatory indicators [C-reaction protein (CRP), interleukin-6 (IL-6), IL-8 and tumor necrosis factor α (TNF-α)], immune indicators (IgA and IgG) and serum amylase recovery time; and (4) study design: randomized controlled trials (RCTs).

Exclusion criteria: (1) research type: review, guideline, systematic review, animal experiment, cell experiment; (2) research content inconsistent with the theme and the full text unavailable; (3) duplicate studies.

Definitions

The diagnosis of AP requires two of the following three criteria: (1) epigastric pain consistent with acute pancreatitis (acute, sudden, persistent and severe abdominal pain that can radiate to the back); (2) serum lipase activity; (3) Enhanced computed tomography (CT)/magnetic resonance imaging (MRI) showed typical AP imaging changes (pancreatic edema or peripancreatic effusion). Cases that met the dignostic criteria of AP with APACHE II score $\geq$ 8, Ranson score $\geq$ 3, CT grade D/E, accompanied by persistent (>48 h) organ dysfunction (especially shock, respiratory disorder, and renal insufficiency) and/or local

TABLE 2 | Summary of the basic characteristics of the included studies.

Reference	Interventions	No. of subjects enrolled	Age (years, mean ± SD)	Sex (M/F)	APACHE II score	Outcomes
He et al. (6)	TPN+Gln	20	39.4 ± 8.6	11/9	Unstates	A, D, E, F, G, K
	TPN	21	40.2 ± 7.8	11/10	Unstates	
Guo et al. (34)	TPN+Gln	20	Unstates	12/8	Unstates	A, G
	TPN	21	Unstates	14/7	Unstates	
Ding et al. (29)	TPN+Gln	10	Unstates	Unstates	Unstates	G, J
	TPN	10	Unstates	Unstates	Unstates	
Fuentes-Orozco (12)	TPN+Gln	22	43.8 ± 14.4	12/10	10.3 ± 1.6	A, C, D, G, I, J
	TPN	22	41.5 ± 14.2	12/10	10.7 ± 1.9	
Gu et al. (32)	TPN+Gln	30	Unstates	Unstates	Unstates	G
	TPN	30	Unstates	Unstates	Unstates	
Tong et al. (41)	EEN+Gln	16	41.5 ± 10.8	10/6	12.1 ± 3.7	B, I, J
	EEN	16	41.9 ± 11.4	9/7	12.1 ± 3.7	
Wang et al. (44)	TPN+Gln	23	Unstates	Unstates	Unstates	A, D, E, F, G, K
	TPN	25	Unstates	Unstates	Unstates	
Huang et al. (35)	TPN+Gln	24	63.6 ± 6.2	18/6	20.8 ± 3.5	B, G, I, J
	TPN	24	62.4 ± 4.8	16/8	21.0 ± 3.2	
Wu et al. (45)	EEN+Gln	15	37.24 ± 3.56	9/6	Unstates	A, D, F, G
	EEN	15	38.61 ± 2.51	10/5	Unstates	
Yang et al. (47)	EEN+Gln	14	42.82 ± 9.02	7/7	9.14 ± 0.77	B, C, D, I, J
	EEN	14	43.25 ± 8.73	7/7	9.21 ± 0.89	
Ran et al. (38)	TPN+Gln	25	54.3 ± 16.2	18/7	9.9 ± 2.4	B, C, D, G, H, I, J
	TPN	25	56.2 ± 15.9	20/5	9.5 ± 2.3	
Jin et al. (36)	EEN+Gln	26	Unstates	Unstates	12.5 ± 4.1	A, B, D, F
	EEN	23	Unstates	Unstates	12.0 ± 5.0	
Singh et al. (52)	EEN+Gln	41	40.78 ± 15.5	24/27	8.7 ± 4.4	A, F
	EEN	39	35.64 ± 13.0	25/14	7.1 ± 2.5	
Wa et al. (42)	EEN+Gln	54	59.3 ± 3.9	28/26	10.4 ± 1.2	B, G, H, I
	EEN	54	62.4 ± 4.1	31/23	10.5 ± 1.2	
Liu et al. (17)	TPN+Gln	24	40 ± 3.96	15/9	Unstates	A, C, D, F
	TPN	23	39.13 ± 4.46	14/9	Unstates	
Lei et al. (37)	EEN+Gln	38	Unstates	Unstates	16.5 ± 1.7	A, B, D, F, I, J, L
	EEN	38	Unstates	Unstates	15.9 ± 2.2	
Yin et al. (49)	TPN+Gln	20	41 ± 3.2	Unstates	Unstates	A, D, E, F, G, K
	TPN	20	41 ± 3.2	Unstates	Unstates	
Wang et al. (43)	EEN+Gln	49	51.85 ± 3.49	29/20	9.59 ± 1.33	G, I
	EEN	49	51.83 ± 3.52	28/21	9.63 ± 1.31	
Yang et al. (46)	EEN+Gln	34	Unstates	22/12	11.98 ± 1.42	I
	EEN	34	Unstates	21/13	12.08 ± 1.36	
Zhao et al. (51)	EEN+Gln	48	58.6 ± 3.8	Unstates	10.6 ± 1.2	B, G, I
	EEN	48	58.6 ± 3.8	Unstates	10.4 ± 1.2	
Cui et al. (28)	EEN+Gln	47	52.7 ± 8.3	32/15	9.7 ± 2.5	G, I, J
	EEN	47	53.5 ± 8.8	34/13	9.8 ± 2.7	
Gao et al. (31)	EEN+Gln	45	47.93 ± 6.24	24/21	Unstates	B, G, I
	EEN	45	48.56 ± 6.37	25/20	Unstates	
Yuan et al. (50)	EEN+Gln	23	51.32 ± 11.65	Unstates	Unstates	I, J
	EEN	24	51.32 ± 11.65	Unstates	Unstates	
Arutla et al. (53)	EEN+Gln	18	38.11 ± 16.3	17/11	8.6 ± 4.5	A, C, D, I
	EEN	22	39.77 ± 15.1	20/2	8.76 ± 3.7	
Ren et al. (39)	EEN+Gln	30	47.95 ± 7.79	21/9	11.34 ± 2.37	A, B, E, F, I, K
	EEN	30	51.71 ± 7.09	25/14	9.73 ± 1.02	

(Continued)

TABLE 2 | Continued

Reference	Interventions	No. of subjects enrolled	Age (years, mean ± SD)	Sex (M/F)	APACHE II score	Outcomes
Sun et al. (40)	EEN+Gln	39	51.71 ± 7.09	25/14	9.73 ± 1.02	G, H
	EEN	39	51.68 ± 7.15	24/15	9.64 ± 1.07	
Chu et al. (27)	EEN+Gln	42	50.62 ± 5.74	27/15	9.76 ± 1.12	G, H, L
	EEN	42	49.48 ± 6.06	26/16	9.63 ± 1.44	
Guan et al. (33)	EEN+Gln	40	58.15 ± 3.13	25/15	Unstates	F, G, I
	EEN	40	58.33 ± 3.2	23/17	Unstates	
Fan et al. (30)	EEN+Gln	46	51.6 ± 3.3	28/18	Unstates	A, B, D, E, F, G
	EEN	46	52.2 ± 2.9	26/20	Unstates	
Yang et al. (48)	EEN+Gln	33	45.51 ± 22.46	17/16	14.03 ± 1.97	B, G, L
	EEN	32	45.52 ± 22.42	16/16	14.17 ± 2.03	

M/F, Male/Female; TPN, Total Parenteral Nutrition; EEN, Enter Enteral Nutrition; Gln, Glutamine; A, Mortality; B, APACHE II score; C, ICU hospital stay; D, Total length of hospital stay; E, Bloating recovery time; F, Complications; G, Liver function index; H, Kidney function index; I, Inflammatory index; J, Immune index; K, Serum amylase recovery time; L, Response rate. "Total length of hospital stay" refers to the total time spent in hospital for SAP patients, including ICU stay time. "Complications" refers to the number of people with complications from SAP. Regardless of Gln treatment, SAP patients have other diseases caused by disease progression, such as pancreatic pseudocyst, peripancreatic infection, abdominal infection, multiple organ failure, sepsis, and gastrointestinal bleeding. "Response rate" refers to whether it improves the overall treatment effect of severe acute pancreatitis and improves the severity of SAP patients (For example, after 2 weeks of treatment, the patient's symptoms such as abdominal pain and bloating were significantly relieved, and laboratory indicators such as blood/urine amylase, blood routine, liver function, and inflammatory factors were significantly improved).

complications (pancreatic necrosis, abscess, and pseudocyst) were diagnosed as SAP (1).

Literature Screening and Data Extraction

Literature screening and data extraction were carried out by two researchers (Dong and Zhao), and any disagreements were resolved through third-party consultation (Li). A table was used to extract the relevant data of the included literature, including: (1) basic information of the study: first author, publication year, sample size, age, and gender ratio; (2) intervention measures: with or without Gln; (3) outcome indicators: mortality, APACHE II score, ICU hospital stay, total length of hospital stay, complications, bloating recovery time, liver function indicators, kidney function indicators, inflammatory indicators, immune indicators, and serum amylase recovery time.

Literature Quality Assessment

The quality of each included study was assessed by the two investigators using tools in the Cochrane Handbook for the Systematic Review of Interventions (23). The evaluation content was divided into six aspects: (1) whether the random allocation method is correct; (2) whether the concealment of the allocation scheme is correct; (3) whether blinding is used; (4) whether the data results are complete; (5) whether there is selective reporting of research results; (6) whether there are other sources of bias.

Statistical Analysis

All studies were analyzed using Review Manager version 5.3 and Stata 12SE. The Odd Ratio (OR) was used as the effect index for dichotomous variables, and the mean difference (MD) or standard mean difference (SMD) for continuous variables. Its estimates and 95% confidence interval (CI) were provided. The chi-square (χ^2) and I^2 tests were used to evaluate the heterogeneity. If significant heterogeneity was present among studies ($P < 0.10$ and $I^2 > 50\%$), a random-effects model was used; otherwise, a fixed-effects model was used (25). Sensitivity analysis was used to analyze sources of heterogeneity. A P-value < 0.05 was statistically significant. Potential publication bias was assessed with funnel plots and Egger's test (26).

RESULTS

Literature Search Results

A total of 1,201 related literatures were initially retrieved from the above databases. After screening, browsing the titles and abstracts, and reading the full texts, we finally included 30 RCTs (6, 12, 17, 27–53). The experimental group (nutritional support containing Gln) included 915 patients, and the control group (conventional nutritional support) included 917 patients. The PRISMA flow chart for literature screening is shown in **Figure 1**. The basic characteristics of the included studies are shown in **Table 2**.

Risk of Bias Assessment Results

Given the risk of bias in the published literature, the included studies were analyzed separately for bias to determine the impact on the conclusions. Two authors independently assessed the included RCTs according to the tools of the Cochrane Systematic Review. The quality assessment of the included studies is shown in **Figures 2**, **3**.

Outcomes of the Intervention

The intervention outcomes were divided into primary and secondary outcomes; the primary outcomes included mortality (**Figure 4**), APACHE II score (**Figure 5**), ICU hospital stay (**Figure 6**), total length of hospital stay (**Figure 7**), bloating recovery time (**Figure 8**) and complications (**Figure 9**), and secondary outcomes included liver function indicators (**Figures 10**–**13**), kidney function indicators (**Figures 14**, **15**), inflammatory indicators (**Figures 16**–**19**), immune

FIGURE 2 | Risk of bias summary.

indicators (**Figures 20**, **21**), serum amylase recovery time (**Figure 22**), and response rate (**Figure 23**). In **Figures 4**–**23**, "experimental" represents the parenteral or enteral nutrition group supplemented with Gln, and "control" means the conventional nutrition group. Rhombuses in the forest plot represent the results of the meta-analysis; the center of the rhombuses represents the point estimates of the effect size of the summary results, such as the OR value, MD value and SMD value, and the width of the rhombuses represents the 95% CIs of the effect size of the pooled results.

Primary Outcomes

Mortality

The effect of adding Gln on the mortality of SAP patients was repored in 13 included studies ($n = 688$ patients). A fixed-effects model was selected since no significant heterogeneity was present among the studies ($P = 0.91$, $I^2 = 0\%$). The pooled results showed that Gln supplementation significantly reduced patient' mortality (OR = 0.38, 95% CI: 0.21–0.69, $P = 0.001$; **Figure 4**). We performed an additional subgroup analysis by stratifying parenteral nutrition vs. enteral nutrition. Compared with the conventional nutrition group, enteral nutrition with Gln failed to effectively reduce the mortality of SAP patients (OR = 0.64, 95% CI: 0.30–1.37, $P = 0.25$), while parenteral Gln supplementation could significantly reduce patient mortality (OR = 0.19, 95% CI: 0.07–0.51, $P = 0.001$).

APACHE II Score

Twelve studies involving 802 patients reported the APACHE II score outcome. Given that significant heterogeneity was present among these studies ($P < 0.00001$, $I^2 = 88\%$), a random-effects model was used. The pooled results indicated that Gln supplementation effectively reduced the APACHE II score compared to the conventional nutrition group (SMD = −1.14, 95% CI: −1.52 to −0.76, $P < 0.00001$; **Figure 5**).

ICU Hospital Stay

ICU hospital stay was reported in five included studies involving 209 patients. There was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 89\%$), which was not reduced after removing one study at a time for sensitivity analysis; accordingly, a random-effects model was selected. The pooled results indicated that Gln supplementation was associated with a significantly shorter ICU hospital stay (SMD = −0.93, 95% CI: −1.83 to −0.04, $P = 0.04$; **Figure 6**).

Total Length of Hospital Stay

An association between the total length of hospital stay and Gln supplementation was reported in twelve studies involving 585 patients. There was significant heterogeneity between these studies ($P < 0.0001$, $I^2 = 73\%$), and, a random-effects model was applied. The pooled results showed that Gln supplementation significantly reduced the total length of hospital stay (MD = −3.41, 95% CI: −4.93 to −1.88, $P < 0.0001$; **Figure 7**). After subgroup analysis by stratifying enteral vs. parenteral supplementation, the modalities of Gln supplementation and the inclusion criteria of the Ran et al. study (32) were found to be the main source of heterogeneity. Furthermore, subgroup analysis showed both parenteral (MD = −4.14, 95% CI: −7.69 to −0.59, $P = 0.02$) and enteral supplementation (MD = −2.78,

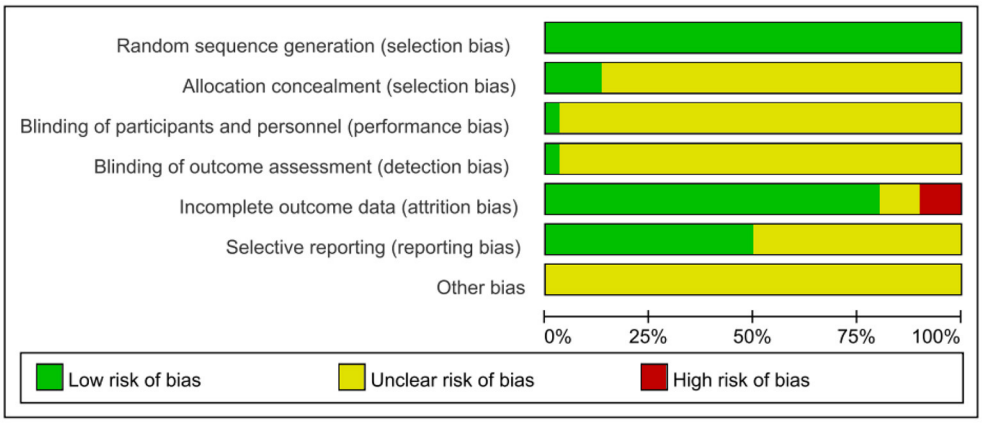

FIGURE 3 | Risk of bias graph.

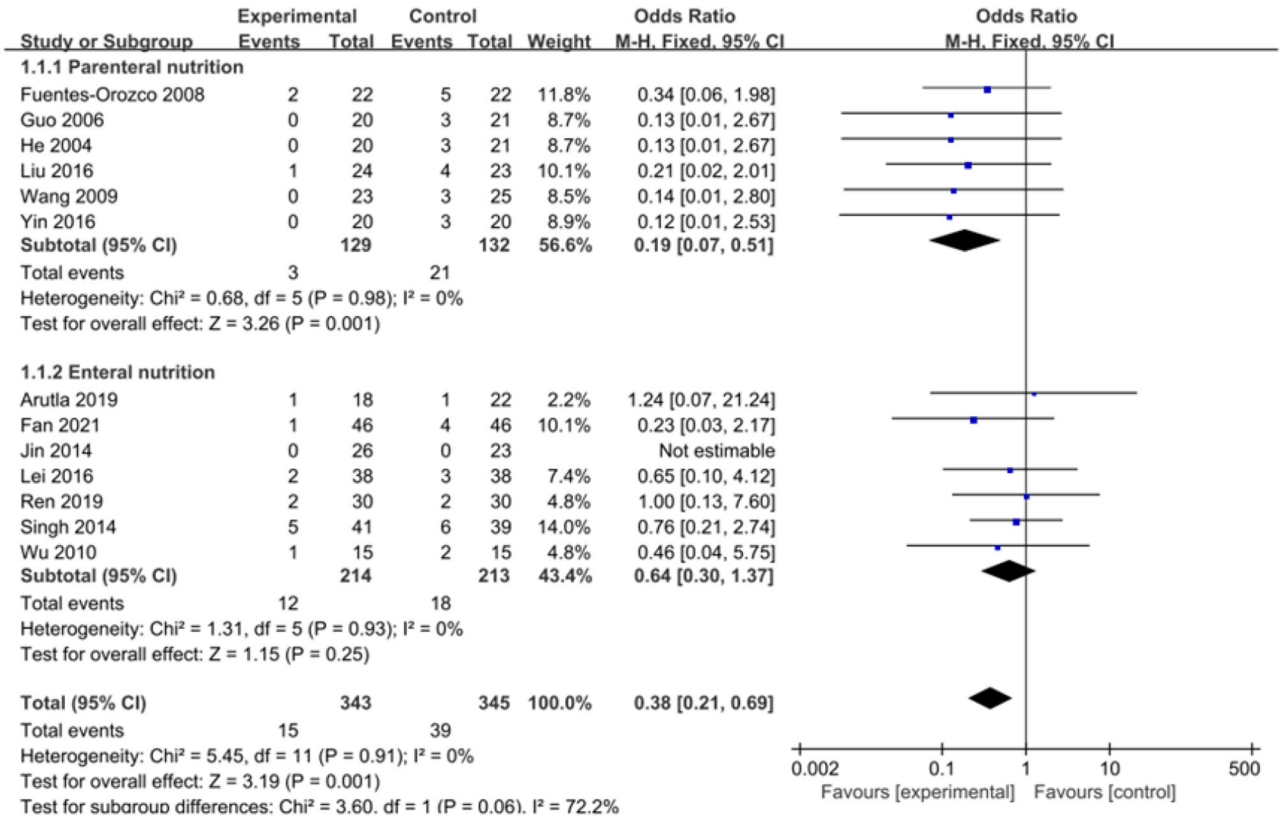

FIGURE 4 | Forest plots of mortality associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and P are the criteria for the heterogeneity test, ♦, pooled odds ratio; —■—, odds ratio, and the edges of ♦, 95% CI.

95% CI: −3.39 to −2.17, $P < 0.00001$) can effectively reduce the total hospitalization time of patients compared with the conventionally nutrition group.

Bloating Recovery Time

To compare the effect of Gln on bloating recovery time in patients, five studies involving a total of 281 patients were included. There was significant heterogeneity among these studies ($P < 0.0001$, $I^2 = 85\%$), and a random-effects model was used. The pooled results showed that Gln supplementation significantly shortened the bloating recovery time in patients (MD = −1.27, 95% CI: −1.44 to −1.10, $P < 0.00001$; **Figure 8**).

Complications

Eleven included studies involving 646 patients reported complications as an outcome, involving 646 patients. No

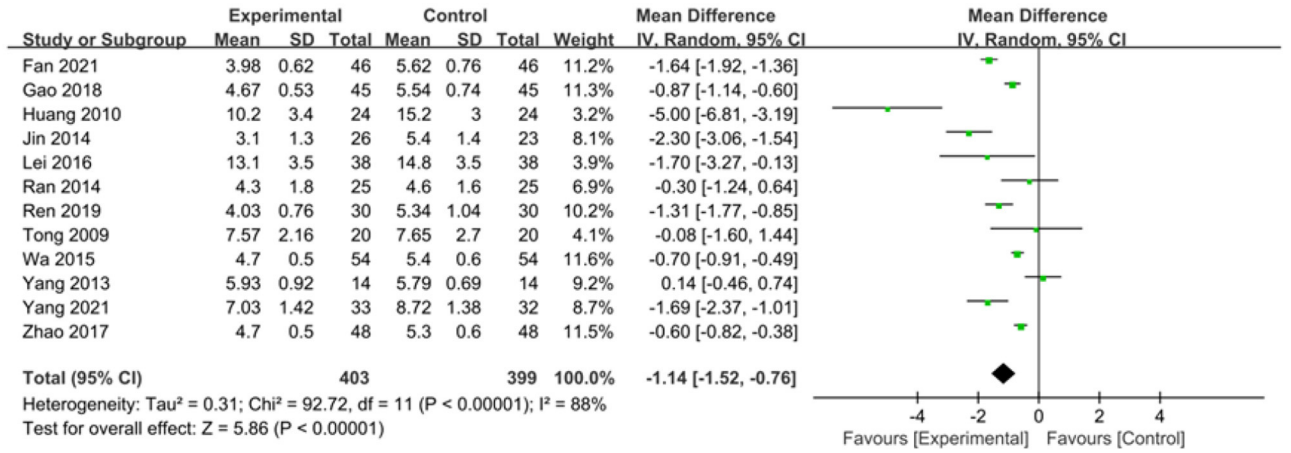

FIGURE 5 | Forest plots of APACHE II score associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

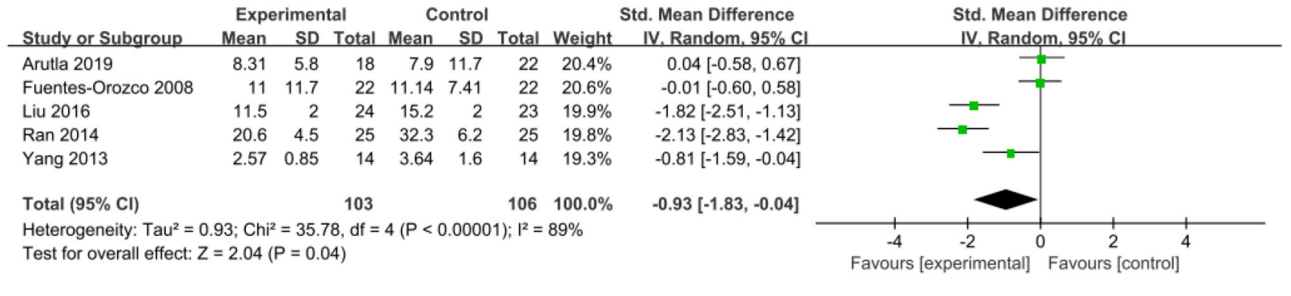

FIGURE 6 | Forest plots of ICU hospital stay associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

significant heterogeneity was found among these studies ($P = 0.13$, $I^2 = 33\%$). The pooled rates showed that Gln supplementation significantly reduced the incidence of complications in patients (OR = 0.45, 95% CI: 0.31–0.66, $P < 0.0001$; **Figure 9**). A subgroup analysis showed that compared with the conventional nutrition group, Gln parenteral supplementation (OR = 0.21, 95% CI: 0.10–0.43, $P < 0.0001$), and enteral nutrition could significantly reduce complications in SAP patients (OR = 0.63, 95% CI: 0.40–0.98, $P = 0.04$), and no significant heterogeneity was found among the included studies ($I^2 = 0$).

Secondary Outcomes

Liver Function Indicators

Serum albumin. An association between serum albumin and Gln supplementation was reported in 15 included studies ($n = 917$). The pooled estimates showed that Gln supplementation significantly increased serum albumin level (SMD = 1.02, 95% CI: 0.74–1.31, $P < 0.00001$; **Figure 10**). However, there was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 75\%$). Substratification into parenteral and enteral subgroups failed to reduce the heterogeneity, suggesting that Gln supplementation was not a source of heterogeneity. Subgroup analysis showed that parenteral (SMD = 0.89, 95% CI: 0.48–1.31, $P < 0.0001$) and enteral Gln supplementation significantly increased serum albumin level (SMD = 1.12, 95% CI: 0.72–1.52, $P < 0.00001$) compared with the conventional nutrition group.

ALT. Six studies reported ALT for the two groups, involving 554 patients with severe pancreatitis, and there was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 97\%$). After conducting a sensitivity analysis, the heterogeneity was not reduced. Accordingly, the heterogeneity was attributed to differences in detection instruments (**Supplementary Material 1**). We selected a random-effects model, and the pooled estimates suggested that Gln supplementation significantly reduced ALT level (MD = −13.73, 95% CI: −16.40 to −11.07, $P < 0.00001$; **Figure 11**).

AST. AST was reported in 3 included studies involving a total of 270 patients. A random-effects model was used since significant heterogeneity was observed among these studies ($P < 0.00001$, $I^2 = 99\%$). The meta-analysis results showed that Gln

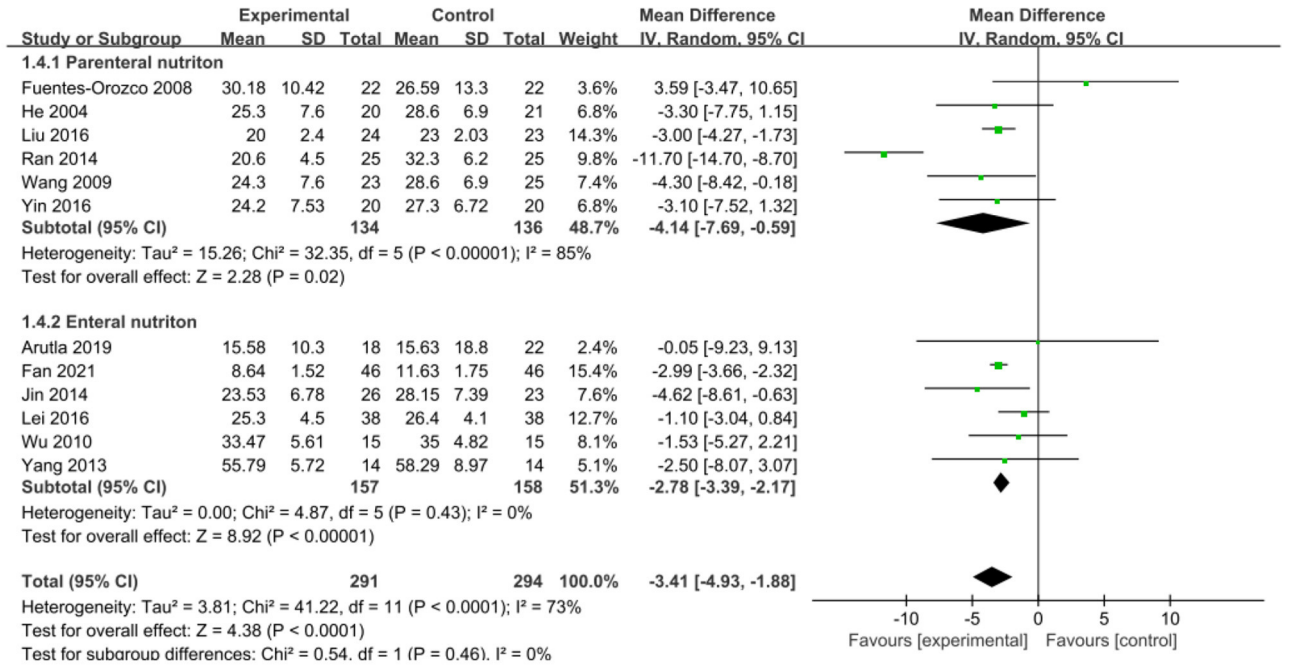

FIGURE 7 | Forest plots of total length of hospital stay associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

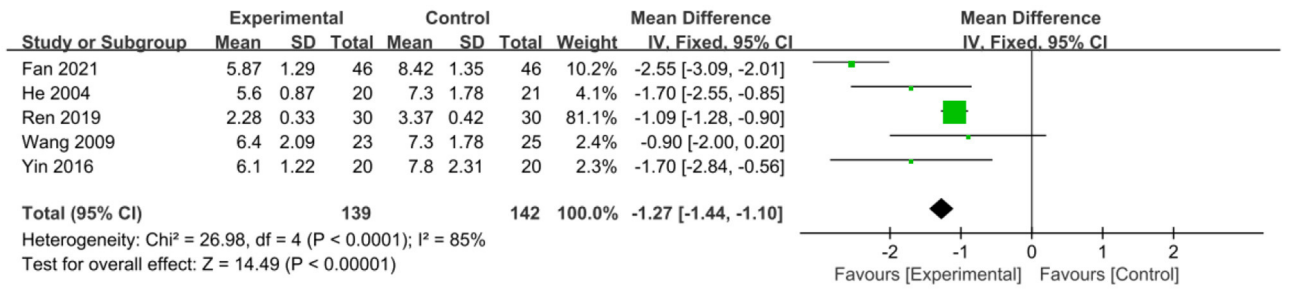

FIGURE 8 | Forest plots of bloating recovery time associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

supplementation was more effective in reducing AST level (MD = −21.45, 95% CI: −34.74 to −8.16, $P = 0.002$; **Figure 7**).

TBIL. Four studies with a total of 392 patients reported TBIL. There was little heterogeneity among these studies ($P = 0.93$, $I^2 = 0\%$), and a fixed-effects model was used. The pooled results suggested that Gln supplementation significantly reduced TBIL level (MD = −5.02, 95% CI: −5.34 to −4.71, $P < 0.00001$; **Figure 13**).

Kidney Function Indicators

Scr. Four studies involving 320 patients were included to assess the effect of Gln supplementation on Scr levels. Significant heterogeneity was observed among these studies ($P = 0.0001$, $I^2 = 86\%$) and a random-effects model was selected. The pooled results suggested that Gln addition was effective in reducing Scr levels (MD = −12.60, 95% CI: −21.97 to −3.24, $P = 0.008$; **Figure 14**).

BUN. Four studies, including 320 patients, reported BUN results. There was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 92\%$) and a random-effects model was used. The combined results indicated that the addition of Gln was not significantly correlated with BUN levels (MD = −1.34, 95% CI: −2.87 to 0.18, $P = 0.08$; **Figure 15**).

Inflammatory Indicators

CRP. Seven studies involving a total of 317 patients reported this outcome. There was large heterogeneity among these studies ($P < 0.00001$, $I^2 = 88\%$), and the pooled estimates suggested that Gln

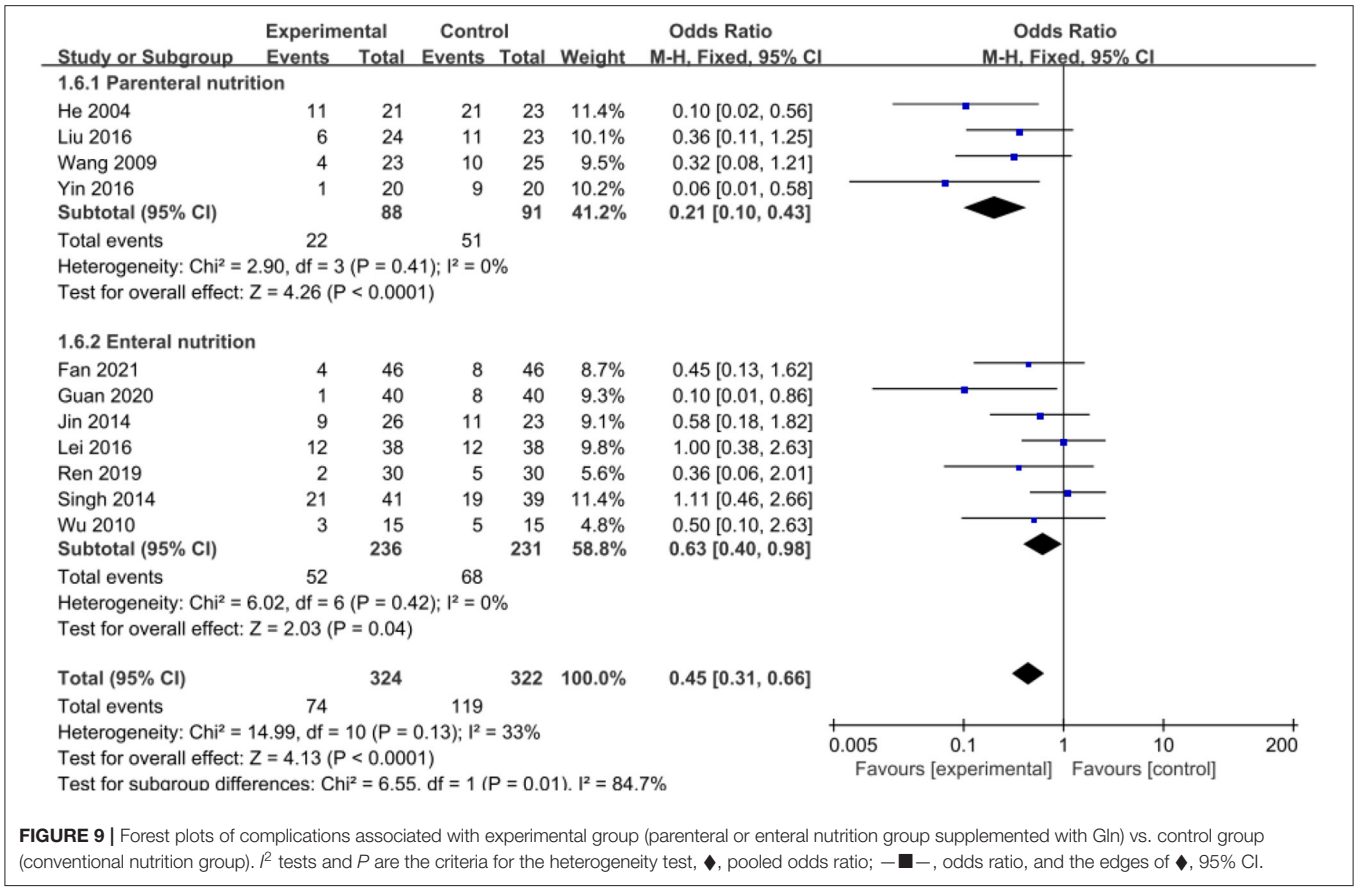

FIGURE 9 | Forest plots of complications associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and P are the criteria for the heterogeneity test, ♦, pooled odds ratio; —■—, odds ratio, and the edges of ♦, 95% CI.

supplementation effectively reduced CRP levels in SAP patients (SMD = −1.67, 95% CI: −2.43 to −0.90, $P < 0.0001$; **Figure 16**). After substratification into parenteral and enteral group, we found that the feeding route was a source of heterogeneity. Our subgroup analysis showed that compared with the conventional nutrition group, both parenteral (SMD = −1.27, 95% CI: −1.66 to −0.87, $P < 0.00001$) and enteral Gln significantly reduced CRP levels (SMD = −2.00, 95% CI: −3.47 to −0.52, $P = 0.008$).

IL-6. IL-6 was reported in 12 studies involving 897 patients. There was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 89\%$) and a random-effects model was used. The results indicated that Gln supplementation effectively reduced IL-6 levels (SMD = −1.23, 95% CI: −1.68 to −0.78, $P < 0.00001$; **Figure 17**).

IL-8. To compare the effects on IL-8 levels in patients, five studies involving 427 patients were included. There was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 93\%$), and a random-effects model was used. The pooled results suggested that Gln supplementation effectively reduced IL-8 level (SMD = −2.04, 95% CI: −2.93 to −1.14, $P < 0.00001$; **Figure 18**).

TNF-α. To compare the effect of Gln supplementation on TNF-α level in SAP patients, 10 studies involving 817 patients were included. Given that significant heterogeneity was observed among these studies ($P < 0.00001$, $I^2 = 95\%$), we applied a random-effects model. The combined results showed that nutritional supplementation with Gln was effective in reducing TNF-α levels (SMD = −2.47, 95% CI: −3.27 to −1.66, $P < 0.00001$; **Figure 19**).

Immune Indicators

IgA. IgA was reported in three studies involving 114 patients. Given that there was significant heterogeneity among these studies ($P < 0.00001$, $I^2 = 94\%$), a random-effects model was selected. The results indicated no statistically significant difference in IgA levels between the Gln supplementation group and the conventional nutrition group (SMD = 1.42, 95% CI: −0.41 to 3.25, $P = 0.13$; **Figure 20**).

IgG. This outcome was reported in 3 included studies involving 118 patients. A fixed-effects model was used since no significant heterogeneity was observed among these studies ($P = 0.19$, $I^2 = 40\%$). The pooled estimates suggested that Gln supplementation can significantly increase IgG levels (MD = 1.24, 95% CI: 0.82–1.67, $P < 0.00001$; **Figure 21**).

Serum Amylase Recovery Time

Serum amylase recovery time was included in four studies, involving 118 patients. There was significant heterogeneity among these studies ($P = 0.002$, $I^2 = 80\%$) and a random-effects

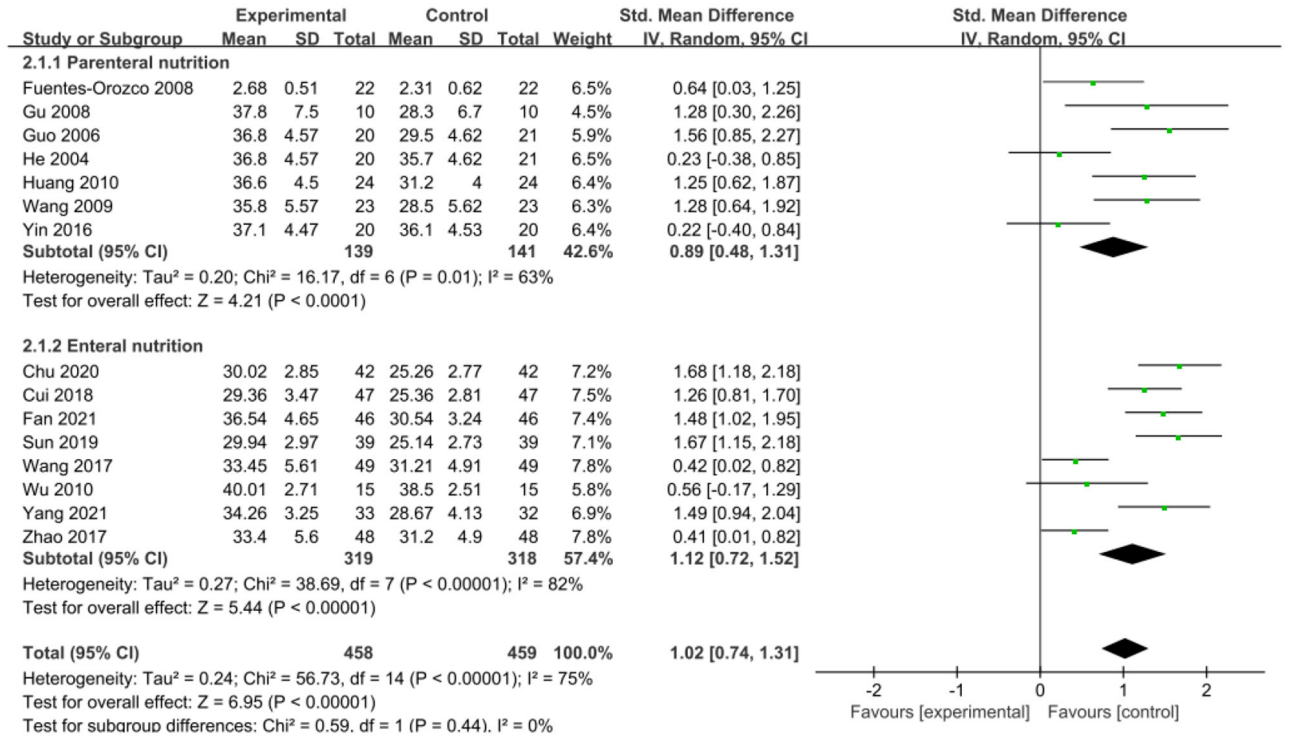

FIGURE 10 | Forest plots of serum albumin associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

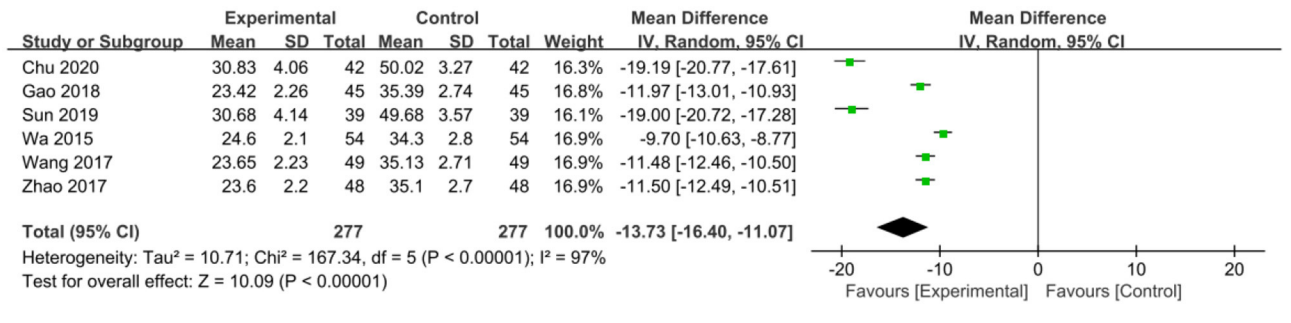

FIGURE 11 | Forest plots of ALT associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

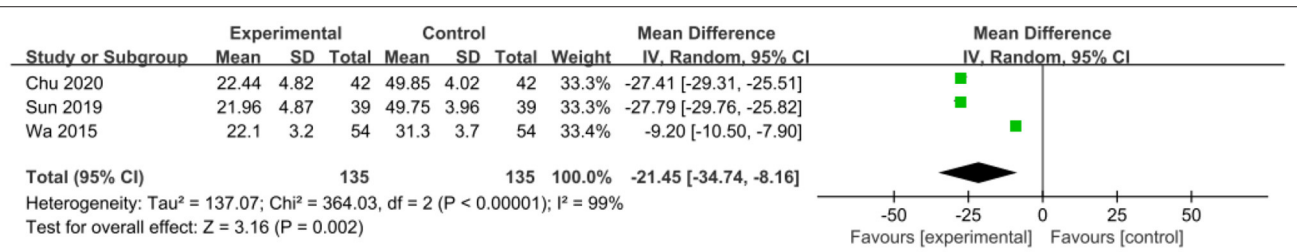

FIGURE 12 | Forest plots of AST associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

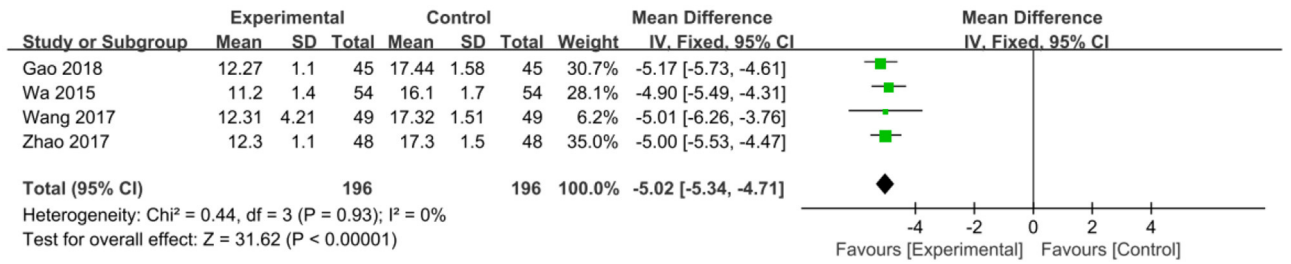

FIGURE 13 | Forest plots of TBIL associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and P are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

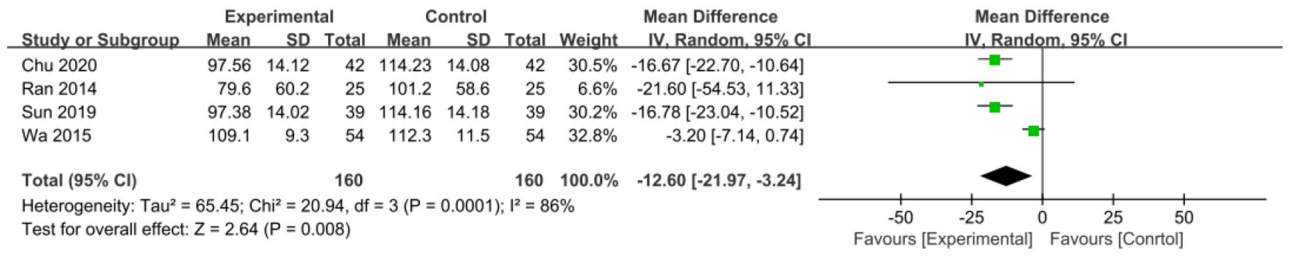

FIGURE 14 | Forest plots of Scr associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and P are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

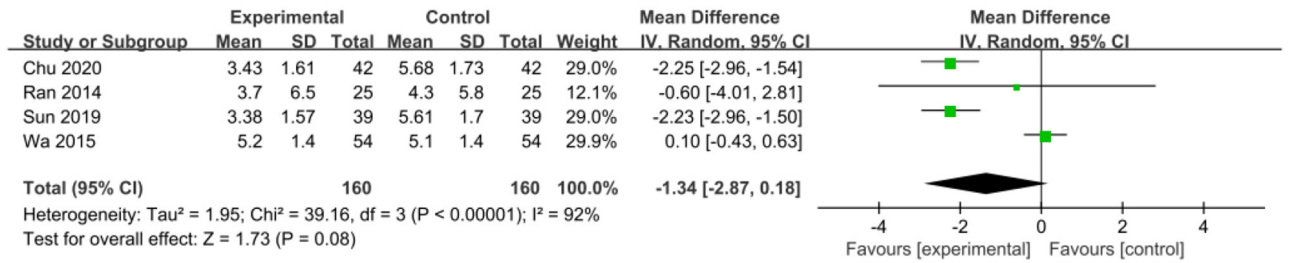

FIGURE 15 | Forest plots of BUN associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and P are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

model was used. The pooled results indicated no significant difference in serum amylase recovery time between treatment with or without Gln supplementation (MD = 0.18, 95% CI: −0.60 to 0.96, $P = 0.65$; **Figure 22**).

Response Rate

Three included studies involving 225 patients reported the response rate. Little heterogeneity was observed among these studies ($P = 0.84$, $I^2 = 0\%$), and, a fixed-effects model was used. The pooled results showed that the response rate between Gln-supplementation and the control group was statistically significant (OR = 4.63, 95% CI: 2.00–10.71, $P = 0.0003$; **Figure 23**).

Sensitivity Analysis

Sensitivity analyses were performed by omitting one study at a time. During analysis of kidney function indicators, when the study of Wa et al. (36) was excluded, the pooled estimates showed that Gln supplementation was more effective in reducing BUN levels than the control group (MD: −2.20, 95%CI, −2.71 to −1.70, $P < 0.00001$), which was inconsistent with the preliminary results and significantly reduced heterogeneity ($I^2 = 0\%$). In terms of serum amylase recovery time, when we excluded the study by Ren et al. (33), the pooled results showed that Gln supplementation failed to effectively reduce the serum amylase recovery time (MD: 0.50; 95% CI, 0.10–0.90; $P < 0.00001$), but the heterogeneity ($I^2 = 0\%$) was significantly reduced.

Publication Bias

Funnel plot and Egger's test were used to evaluate publication bias of mortality, APACHE II score, complications, total length of hospital stay, serum albumin, IL-6, and TNF-α. The results showed significant publication bias for mortality (Egger's test, $P = 0.025$), complications (Egger's test, $P = 0.000$), and TNF-α (Egger's test, $P = 0.020$). However, no significant publication bias was observed for in the APACHE II score (Egger's test, P

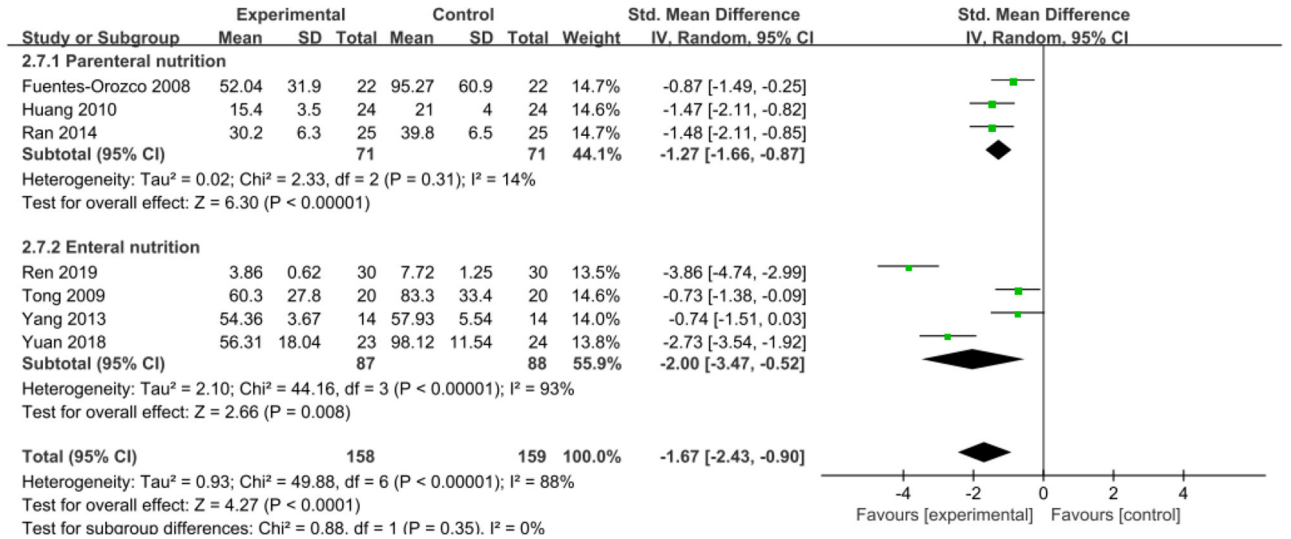

FIGURE 16 | Forest plots of CRP associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

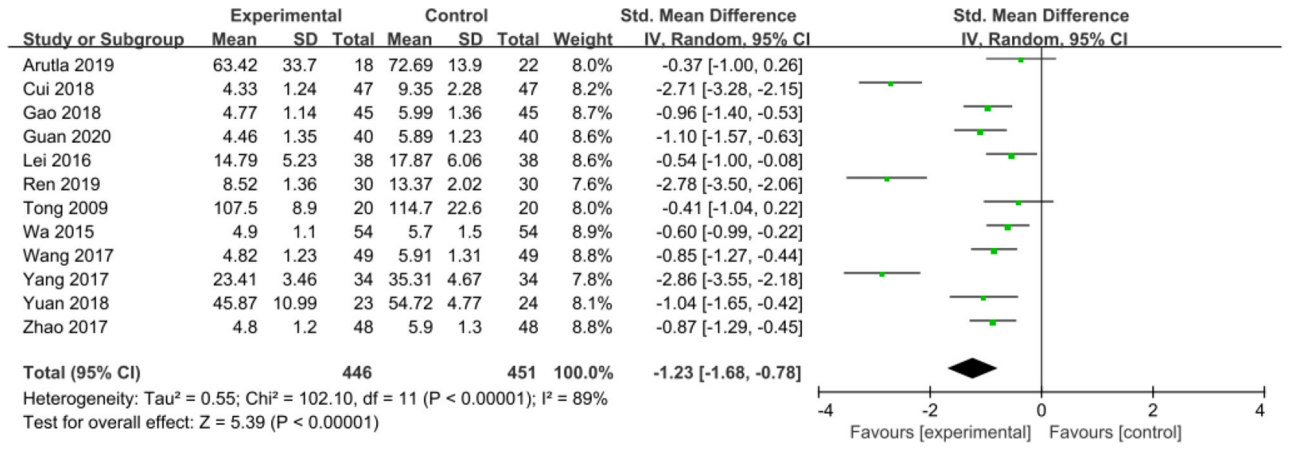

FIGURE 17 | Forest plots of IL-6 associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

= 0.262), total length of hospital stay (Egger's test, $P = 0.892$), serum albumin (Egger's test, $P = 0.545$), and IL-6 (Egger's test, $P = 0.059$) (**Figure 24**).

DISCUSSION

The meta-analysis aimed to evaluate the efficacy of Gln parenteral or enteral nutrition vs. conventional nutrition in patients with SAP. Outcomes, such as mortality, complications, the hospital stay of SAP patients, and other test results, were evaluated.

Consistent with the literature, we found that nutritional support with Gln may be an effective therapeutic approach for SAP. Importantly, unlike enteral Gln supplementation (OR = 0.64, 95% CI: 0.30–1.37, $P = 0.25$), parenteral nutrition with Gln effectively reduced mortality (OR = 0.19, 95% CI: 0.07–0.51, $P = 0.001$), which was inconsistent with the study by Jiang et al. (14) who reported that enteral Gln supplementation could significantly reduce the mortality risk (risk ratio= 0.38; 95% CI, 0.16–0.90; $p = 0.03$). Accordingly, future clinical studies are warranted to validate this finding. Regarding the total length of hospital stay and complications, both parenteral and enteral Gln supplementation were more effective than conventional nutrition ($P < 0.05$). Interestingly, we found that when a Gln concentration of 0.4 g/kg used in 17 included studies (6, 12, 27, 28, 30, 31, 33–35, 37, 40, 42–45, 48, 49, 51) for parenteral supplementation

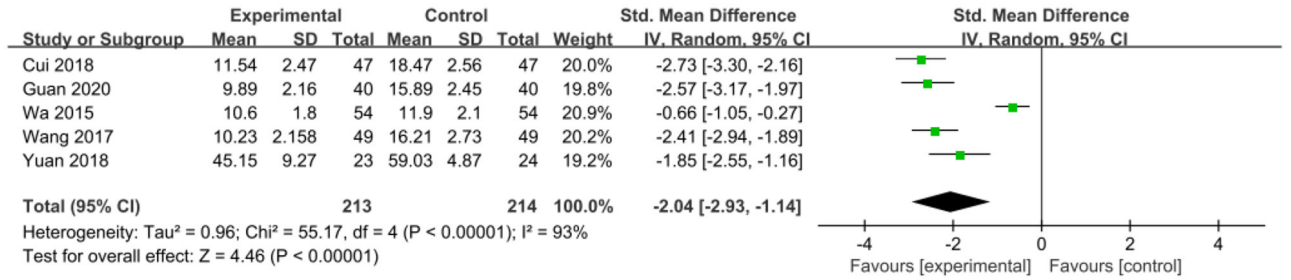

FIGURE 18 | Forest plots of IL-8 associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

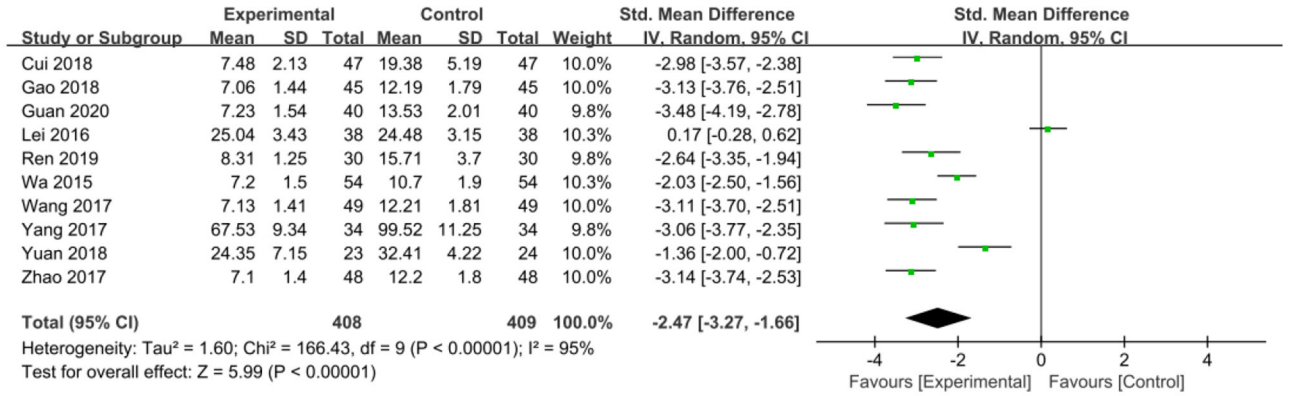

FIGURE 19 | Forest plots of TNF-α associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

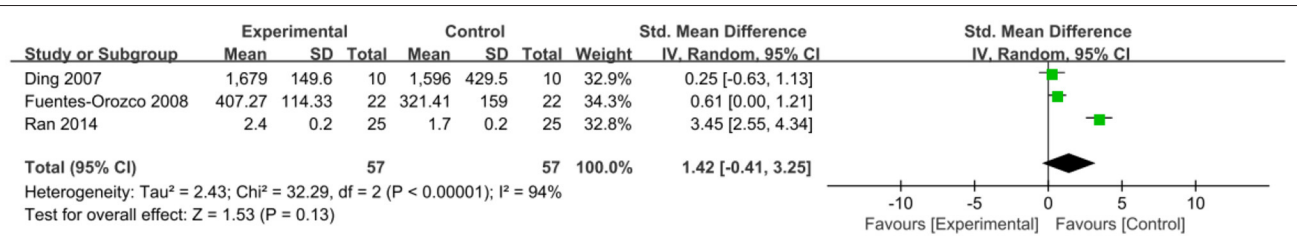

FIGURE 20 | Forest plots of IgA associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled standard mean difference; —■—, standard mean difference, and the edges of ♦, 95% CI.

did not reduce the total hospital stay ($P > 0.05$), compared to enteral supplementation ($P < 0.05$; **Supplementary Material 3**). However, parenteral Gln supplementation was more effective than enteral supplementation in reducing the incidence of complications (**Supplementary Material 3**). In terms of APACHE II score, ICU hospital stay and bloating recovery time, Gln supplementation was more effective than conventional nutrition ($P < 0.05$). Nonetheless, given the limited number of included studies, subgroup analysis could not be performed. 0.4 g/kg Gln yield results, emphasizing the need for future research with large sample data. As for secondary outcomes, in terms of liver function indicators, nutritional support therapy with Gln effectively improved liver function ($P < 0.05$). Moreover, we found that Gln supplementation (enteral or parenteral nutrition) increased serum albumin levels. We further analyzed the pros and cons of different methods of 0.4 g/kg Gln supplementation and found that parenteral supplementation was inferior to as enteral supplementation (**Supplementary Material 3**). Interestingly, compared with the conventional nutrition group, Gln supplementation could effectively reduce Scr levels (MD $= -12.60$, 95% CI: -21.97 to -3.24, $P = 0.008$). However, BUN results were not consistent with the above findings (MD $= -1.34$, 95% CI: -2.87 to 0.18, $P = 0.08$), and this discrepancy may be attributed to the quality of the included literature. Gln

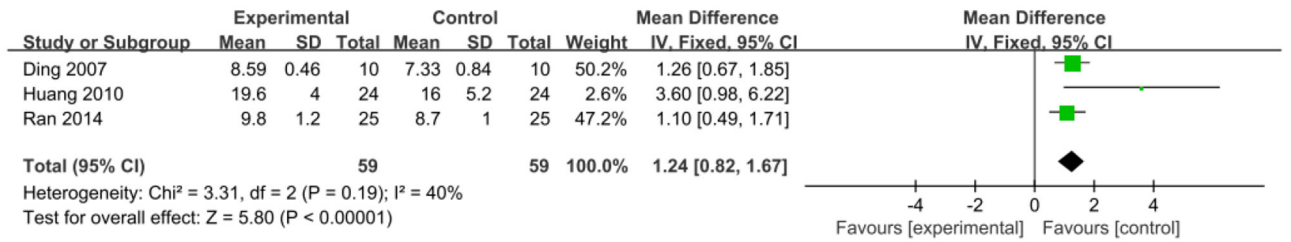

FIGURE 21 | Forest plots of IgG associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

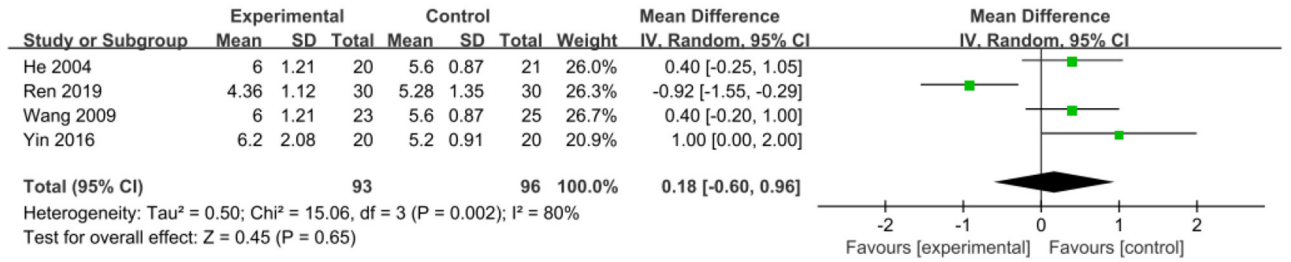

FIGURE 22 | Forest plots of serum amylase recovery time associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled mean difference; —■—, mean difference, and the edges of ♦, 95% CI.

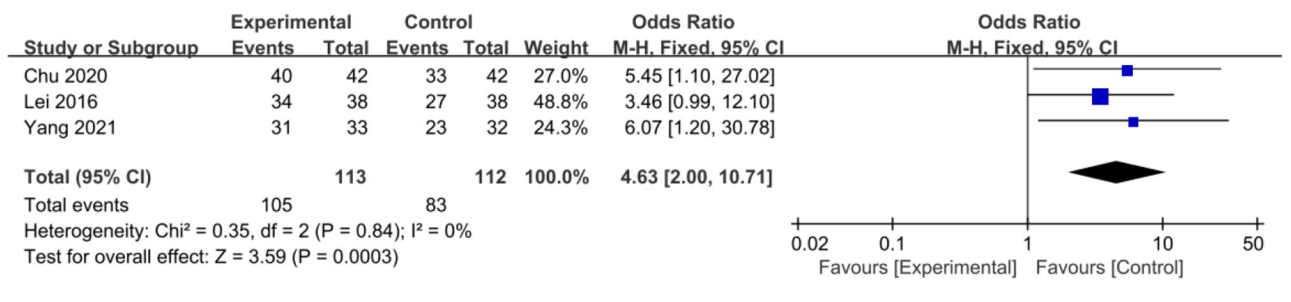

FIGURE 23 | Forest plots of response rate associated with experimental group (parenteral or enteral nutrition group supplemented with Gln) vs. control group (conventional nutrition group). I^2 tests and *P* are the criteria for the heterogeneity test, ♦, pooled odds ratio; —■—, odds ratio, and the edges of ♦, 95% CI.

supplementation was more effective than conventional nutrition in reducing the inflammatory indicators, including CRP, IL-6, IL-8, and TNF-α, and could effectively alleviate the inflammatory state in SAP. However, in terms of immune indicators, Gln therapy significantly improved IgG levels (MD = 1.24, 95% CI: 0.82–1.67, $P < 0.00001$), but no statistically significant differences in IgA were observed (SMD = 1.42, 95% CI: −0.41 to 3.25, $P = 0.13$). In addition, no significant difference in serum amylase recovery time was observed between the two groups ($P > 0.05$).

In this meta-analysis, Gln supplementation was effective for all parameters except BUN, IgA and serum amylase recovery time. During the subgroup analysis, except for mortality, the nutrition route did not affect the outcome of corresponding indicators. At the similar Gln concentrations (0.4 g/kg), the two supplementation methods did not change mortality, suggesting that parenteral supplementation was more effective for SAP patients. Indeed, notwithstanding that parenteral Gln supplementation was inferior to enteral supplementation in terms of total hospital stay and serum albumin levels, parenteral supplementation was associated with a lower incidence of complications in SAP patients. Although some biochemical parameters, such as CRP, serum albumin and Scr, improved with Gln use, there were no significant changes in primary outcomes, such as mortality (with enteral supplementation). It has been established that the systemic inflammatory response in AP causes an increase in calorie and protein metabolism, which leads to systemic organ damage and substantial nutrient loss, and long-term fasting aggravates the negative nitrogen balance (54). Inflammatory storms and inadequate nutrient intake can exacerbate organ damage and intestinal dysfunction. Moreover, peripancreatic infection and necrosis cause severe sepsis, further

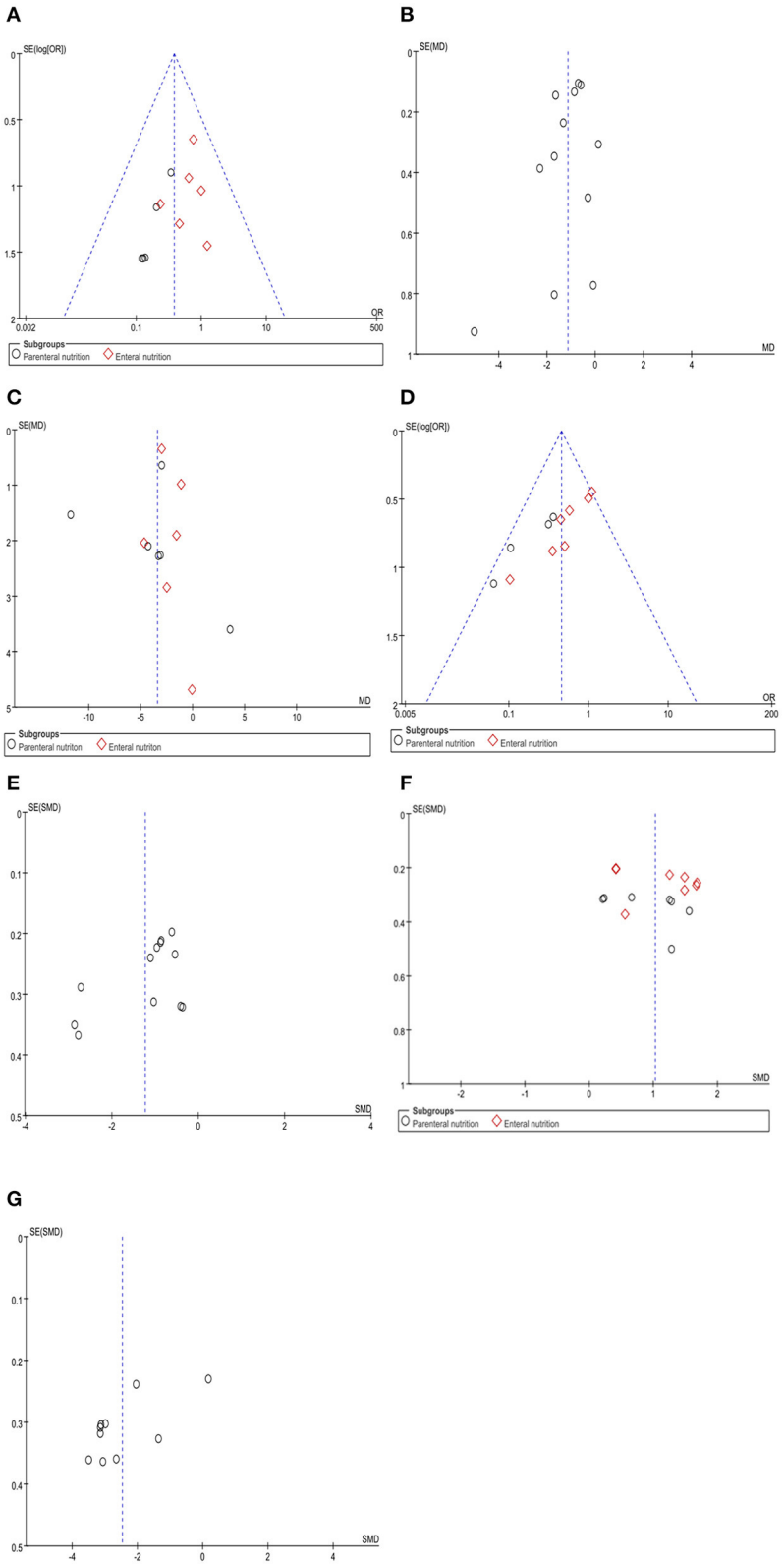

FIGURE 24 | Funnel plots of the included studies for mortality **(A)**, APACHE II score **(B)**, total length of hospital stay **(C)**, complications **(D)**, serum albumin **(F)**, IL-6 **(E)**, and TNF-α **(G)**.

disrupting the intestinal barrier and leading to high patient mortality. Therefore, protecting the integrity of the intestinal barrier is critical for reducing patient mortality and improving primary clinical outcomes. In the present study, we found that enteral Gln supplementation did not improve the mortality of SAP patients, which may be attributed to the non-recovery of the intestinal function, and intestinal absorption of Gln was significantly lower than that of intravenous infusion. For patients with very severe symptoms, Gln yielded no significant effects in the short term. In addition, although the effect of enteral supplementation of Gln can be effective, it is still inferior to parenteral nutrition, which is mainly related to whether Gln is effectively utilized during early stages. The current study found that parenteral supplementation was more effective than enteral supplementation on primary and secondary outcomes. However, a limited number of studies were included, and the severity of SAP patients and the timing, dose, and duration of Gln use remain primarily understudied, warranting further studies.

Our study findings are consistent with previous meta-analyses (14, 22). Seven RCTs were included in the meta-analysis by Jiang et al. (14), with a relatively smaller number of patients and outcomes involved. A meta-analysis by Li et al. (22), which included 10 RCTs showed that compared with enteral nutrition (SMD = 0.36, 95% CI: −0.08 to 0.80, $P > 0.05$), intravenous infusion Gln was more effective in reducing plasma albumin levels (SMD = 1.19, 95% CI: 0.62–1.77, $P < 0.05$), which was inconsistent with our study, and different results were also observed with CRP In the present meta-analysis, 30 RCTs were included based on strict inclusion and exclusion criteria with increased sample size, primary and secondary outcomes. We did not analyze indicators with <3 included studies to reduce the risk of bias and ensure the robustness and accuracy of our findings. Morever, we searched eight major databases to ensure that relevant articles were not missed. Finally, we performed a literature quality assessment, sensitivity analysis, and publication bias detection on the included literature and presented the results in forest and funnel plots for a comprehensive meta-analysis.

One strength of this study is that it summarizes and analyzes the latest related literature, which makes up for the knowledge gap in this research field. In addition, we included a relatively large number of RCTs and a large sample size, providing robust evidence for our findings. However, some limitations of our study warrant attention. First of all, some indicators such as BUN were reported in few studies which may be a source of publication bias. Moreover, the reliability of our findings was affected due to differences in detection method. Given the presence of high heterogeneity among the included studies, a random-effects model was used to improve the stability of these outcomes. Finally, since most of the included studies originated from China, the present study's findings cannot be generalized to other regions, emphasizing the need for more studies worldwide.

CONCLUSION

The findings of this study provided compelling evidence that nutritional support therapy with Gln is an effective therapy for SAP, especially for the recovery of relevant biochemical indicators of patients during hospitalization and the reduction of hospitalization time. Subgroup analysis found that parenteral nutrition supplementation with Gln was more likely to reduce mortality and complications in patients, so parenteral nutrition seemed to be a better choice for patients with severe symptoms. However, there are few studies on the timing and dose of Gln supplementation in SAP patients, and prospective trials are needed to prove it. In addition, the outcome of Gln nutrition therapy for some indicators is largely unclear, such as serum amylase and intestinal function recovery time, whether to transfer to surgery, etc. Safety is also the focus of research, including gastrointestinal reactions, metabolic disorders, but it has not been paid attention to in detail in previous studies. In the implementation of medical decisions, clinicians should weigh the patient's condition based on the above factors, so as to facilitate a good prognosis of patients. Further research with larger sample size is needed to improve the current understanding of these clinical outcomes and accurately evaluate the efficacy of nutritional therapy with Gln for SAP patients.

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.

AUTHOR CONTRIBUTIONS

SD: writing—original draft preparation, supervision, and project administration. ZZ: writing—original draft preparation and visualization. XL, ZC, and WJ: writing—review and editing and supervision. WZ: writing—original draft preparation, supervision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Optimal Cutoffs for the Diagnosis of Sarcopenia in Older Chinese Adults

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Background: The optimal criteria for sarcopenia in the older Chinese population have not been defined. Consequently, this study aims to determine the optimal cutoffs of grip strength, appendicular skeletal muscle index (ASMI) using bioelectrical impedance analysis (BIA), and gait speed, comprising the best definition of sarcopenia for older Chinese populations.

Methods: A total of 2,821 (1,398 men and 1,423 women) community-dwelling older people (≥60 years) and 409 (205 men and 204 women) young healthy adults (25–34 years) were recruited from three big cities in China. Besides gait speed and grip strength, we examined ASMI by BIA and dual-energy X-ray absorptiometry (DXA), comprising the three components of sarcopenia. DXA classification for low ASMI, 20th percentile among older adults in the study sample, was found to be best compared with the other existing classification, 1 SD and 2 SD below the mean for the young population, and was used as the gold standard to determine the optimal cutoffs of BIA using receiver operating characteristic curves (ROC). The cutoffs of handgrip strength and gait speed were determined following the same rule.

Results: Using gender-specific 20th percentiles of DXA (6.53 kg/m^2 for men and 5.40 kg/m^2 for women), the cutoffs 7.05 kg/m^2 for men and 5.85 kg/m^2 for women were determined as optimal cutoffs of BIA by achieving the largest sensitivity (0.81, 95% CI: 0.63–0.93 for men and 0.90, 95% CI: 0.73–0.98 for women) and specificity greater than 0.80 (0.80, 95% CI: 0.72–0.87 for men and 0.81, 95% CI: 0.72–0.87 for women) in the ROC analysis. The 28.5 kg and 1.05 m/s for men and 18.6 kg and 1.01 m/s for women were determined as the cutoffs for handgrip strength and gait speed, respectively. Based on the derived cutoffs, 14.2% of men and 15.7% of women in the older Chinese study population were classified as sarcopenia.

Conclusion: Notably, 7.05 kg/m^2, 28.5 kg, and 1.05 m/s for men and 5.85 kg/m^2, 18.6 kg, and 1.01 m/s for women were selected as the optimal cutoffs for low ASMI by BIA, handgrip strength, and gait speed, respectively. These optimal cutoffs will enhance practicability for screening sarcopenia in primary care and clinical settings.

Keywords: sarcopenia, cutoff thresholds, Chinese, older people, dual-energy X-ray absorptiometry, bioelectrical impedance analysis

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INTRODUCTION

Sarcopenia is a well-known geriatric syndrome characterized by loss of skeletal muscle mass with subsequent low muscle strength (1), leading to impaired health with mobility disorders, increased fall and fracture risk, functional decline, frailty, poor quality of life, and even increased mortality risk (2–5).

Sarcopenia was first described in the 1980s as an age-related decline in lean body mass, affecting mobility, nutritional status, and independence (6). However, since skeletal muscle is influenced by factors, such as race, environment, diet, and exercise habits, sarcopenia still lacks internationally agreed diagnostic criteria, although there are a number of consensus diagnoses. The most widely used of these include the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS), and the Asian Working Group on Sarcopenia (AWGS). Notably, the 2011 IWGS consensus on sarcopenia defines sarcopenia only in terms of a reduction in muscle mass and physical activity (7). In contrast, the EWGSOP consensus published in 2010 considered sarcopenia as a syndrome with adverse consequences, such as functional impairment, reduced quality of life, and even death due to progressive and widespread loss of skeletal muscle mass and strength, recommended the use of tests for muscle mass, muscle strength, and physical performance to diagnose sarcopenia, and classified sarcopenia into pre-muscular hyposmia, sarcopenic phase, and severe sarcopenic phase (8). The Foundation for the National Institute of Health (FNIH) Sarcopenia Project defined sarcopenia in 2014 as clinically relevant low muscle strength (weakness) and low lean mass (9). In 2019, the European Working Group on Sarcopenia in Older People (EWGSOP) summarized the clinical and scientific findings of sarcopenia over the past decade and revised the consensus (EWGSOP2), emphasizing low muscle strength as the primary parameter in the evaluation of sarcopenia, stating that muscle strength is a better predictor of poor outcomes than muscle mass. It was noted that muscle strength is a better predictor of poor disease outcomes than muscle mass (10). The Asian Working Group for Sarcopenia (AWGS) guideline also addressed the cutoff points for older Asian people by modifying the EWGSOP guideline (11) and updated as AWGS2 (12) with a cutoff definition and a new definition of possible sarcopenia in 2019. However, mainland Chinese were not included in the study population in both versions of the AWGS consensus, and the representativeness and application of the definition may be limited in both versions. The prevalence of sarcopenia in mainland China could be inaccurately estimated using the AWGS cutoff values.

The reported prevalence of sarcopenia varies widely depending on its definition. Muscle mass measurement in mainland China remains under-investigated and inadequately validated. Limited studies with small sample sizes or limited geographic diversity have proposed cutoff values for low muscle mass and investigated the prevalence of sarcopenia in mainland China (13, 14). Therefore, developing cutoff values based on the local reference population is essential to better understand the current prevalence of sarcopenia in China.

Moreover, muscle mass can be measured by various techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA) (15, 16). Considering cost, portability, and technical skills, MRI and CT are more suitable in clinical settings. Moreover, DXA and BIA are two frequently used methods for population studies, and DXA has been recommended as the preferred detection technology for assessing skeletal muscle loss due to its low radiation, accuracy, and strong clinical feasibility (9, 12, 17). BIA is a more portable, easy-to-use, and inexpensive tool compared with DXA. Emerging evidence supports that BIA is valid in the estimation of body composition using DXA as a reference standard (18). However, these validation studies were not conducted on the Chinese population.

Three components of sarcopenia include a low muscle mass (component 1), a low handgrip strength (component 2), and/or a low gait speed (component 3) according to the AWGS recommendation (11). The optimal criteria for sarcopenia in the older Chinese population have not been defined. Consequently, this study aimed to determine the optimal cutoffs of grip strength, appendicular skeletal muscle index (ASMI) using BIA, and gait speed, comprising the best definition of sarcopenia for older Chinese populations.

METHODS

Study Population

This was a large, multicenter cross-sectional study conducted in 2014–2015 designed to select a representative sample of older Chinese adults (aged ≥60 years) living in urban areas of China to understand the prevalence of sarcopenia in older Chinese adults and also to study the distribution of muscle mass and muscle function in young Chinese adults (aged 25–34 years) for the new criteria of sarcopenia in Chinese people. In brief, this study selected three geographic representative cities (Beijing, Shanghai, and Chengdu) according to the characteristics of the typical life and dietary pattern. After the statistics of communities with similar size and population density in the three cities, one community was selected in each of the three cities according to the random sampling method for sample recruitment. In total, 2,834 older subjects (1,405 men and 1,429 women) participated with a balance in gender. In addition, the number of subjects aged between 60 and 64 years should not exceed one-third of the total target population in each site to match the national population distribution in China. Subjects aged ≥60 years living in the community for more than 12 months with no history of the listed diseases (implanted electronic device or orthopedic metal implantations, hyperthyroidism or hypothyroidism, severe heart dysfunction, renal dysfunction with significant sodium water retention or edema, diuretics intake, and later stage of malignancies with cachexia) were selected as the older reference group.

In addition, 423 young subjects (213 men and 210 women) were recruited from Beijing and Shanghai. The young subjects were healthy men and women aged 25–34 years, had a BMI between 18.5 and 26.9, and with no history of the listed diseases

(diabetes, thyroid diseases, cardiovascular diseases, liver diseases, renal diseases, and active infection of tuberculosis, human immunodeficiency virus, and hepatitis). Subjects who were heavy manual laborers, professional or semiprofessional athletes, and with physical disabilities were excluded from both groups.

This study was approved by the Ethics Committee of the institute at each study site (Peking Union Medical College Hospital, The Sixth People's Hospital Affiliated Shanghai Jiaotong University, and West China Hospital Affiliated to Sichuan University). Written informed consent was obtained from each participant. This study was registered at www.clinicaltrials.gov (NCT02089971 and NCT02089906).

Definitions and Measurements

Sarcopenia

Sarcopenia has been described as an age-related decline in skeletal muscle mass and muscle function (defined by muscle strength or physical performance). The recommended diagnostic algorithm of the AWGS, which includes three components, was applied to assess sarcopenia in this study. Study participants with a low muscle mass (component 1), in which DXA was regarded generally as the gold standard measure, plus a low handgrip strength (component 2) and/or a low gait speed (component 3), were regarded as having sarcopenia according to the AWGS recommendation (11, 12).

Measurements

Anthropometric measurements were examined by standard protocols and instruments. The subjects wore lightweight clothing without shoes. Bodyweight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, on a calibrated scale. Calf circumference was measured at the widest point of the participants' legs using a nonelastic measuring tape.

Appendicular skeletal muscle mass (ASM) was measured using two methods, the BIA method using a calibrated bioelectrical impedance analyzer (Inbody 720, Biospace Co., Ltd, Seoul, Korea) and the DXA method using the DXA scanner (Lunar Prodigy, GE Healthcare, Madison, WI, USA) as previously published (18, 19). Both measurements provided the lean body mass of limbs and trunk, body fat mass, and bone mass for all subjects of the young reference group. All eligible subjects of the older group received body composition measurements by BIA. Approximately 10% of the subjects (290 subjects) were randomly selected to receive a muscle mass measurement using the DXA method. ASM was calculated as the sum of the lean body mass of the limbs, which is a good proxy for whole-body skeletal muscle mass (13). ASMI was calculated as ASMI = ASM/height^2 (kg/m^2).

There are three existing classifications for defining low ASMI based on DXA: first, ASMI below 2 standard deviations (SDs) from the mean of the young population, second, ASMI below 1 SD from the mean of the young population, and the third, ASMI below 20th percentile of the older population (20–25). We compared the three classifications based on the young study sample to define prevalence in the older study sample. The three cutoff points were used to calculate the rate of low skeletal muscle mass in the older Chinese population for identifying the optimal cutoffs by determining a low muscle mass prevalence between 10 and 40% (2, 22, 26–30) and without gender difference. Based on the lowest 20% of older references, 6.53 and 5.40 kg/m^2 in men and women were selected as low ASMI cutoff points.

Muscle function was assessed by measuring handgrip strength and gait speed (13). Muscle grip strength was assessed as the best of three attempts with the dominant hand using a squeezing electronic hand dynamometer (Camry EH101, Zhongshan Camry Electronic Co. Ltd, Guangdong, China). Gait speed was assessed as the average value of two tests using the 6-m walk test at self-selected speed by a trained assessor (31). Following the optimum cutoffs for ASMI, we used the 20th percentiles in the older study sample to define low handgrip strength and low gait speed.

All examinations are performed by uniformly trained clinicians with more than 5 years of clinical trial experience in this field. After training, they are tested to make sure that the results they test are repeatable.

Statistical Analysis

All data analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The two-tailed significance level was set to $p < 0.05$. Considering a relatively low prevalence of 5% and 2% as the maximum tolerable error, a total of 2,988 participants with 10% attrition were planned to be enrolled in this study such that we have at least 2,736 evaluable subjects (456 in each center and gender group). In total, 2,834 (1,405 men and 1,429 women) older participants from three centers were enrolled and were stratified by gender and then by age group (60–64 and ≥65). To develop population-specific reference values for low muscle mass using both BIA and DEXA methods, a total of 400 healthy young Chinese participants were enrolled, 100 participants as recommended in the literature for constructing reference intervals for each gender and two centers.

Demographic characteristics, body measurements, and muscle function measurements were presented as mean and SD for continuous variables with normal distribution and absolute numbers and percentages for enumeration data. Gender-specific prevalence of sarcopenia in the older group was calculated according to six existing cutoff values based on the current guidelines of the FNIH, AWGS (and revision), EWGSOP (and revision), and IWGS (7–12). The prevalence of sarcopenia between genders was compared using the chi-square test or Fisher's exact test. The prevalence of low muscle mass and sarcopenia between BIA and DXA in the same individuals who had both measurements was compared using McNemar's test. A simple linear regression and Bland–Altman analysis were conducted to evaluate the agreement between the BIA and DXA result measurements.

To identify the best cutoffs of BIA in two genders, the receiver operating characteristic (ROC) curve analysis was applied using DXA classification of low ASMI as the gold standard. The area under the receiver operating curves was used to determine the optimal cutoffs of BIA in discriminating low ASMI by achieving maximum sensitivity

TABLE 1 | Characteristics of the young reference group and older participants by gender.

Parameters	Male		Female	
	Young sample (n = 205)	Older sample (n = 1,398)	Young sample (n = 204)	Older sample (n = 1,423)
Age (years)	27.4 ±2.7	68.6 ±6.3	27.5 ±2.8	68.1 ±6.0
Height (cm)	172.3 ±5.7	165.7 ±6.2	160.8 ±5.0	154.0 ±5.9
Weight (kg)	67.6 ±7.9	67.7 ±9.9	54.3 ±5.9	58.8 ±9.4
BMI (kg/m^2)	22.7 ±2.0	24.6 ±3.1	21.0 ±2.03	24.8 ±3.5
Upper arm circumference (cm)	28.6 ±2.5	28.1 ±3.1	25.9 ±2.3	28.0 ±3.4
Total fat mass BIA (kg)	13.7 ±4.5	18.9 ±5.9	15.2 ±4.0	21.8 ±6.3
Total fat mass DXA (kg)	14.7 ±5.2	18.5 ±6.3*	16.4 ±4.1	20.3 ±5.9*
Total body fat percentage BIA (%)	20.1 ±5.1	27.5 ±5.9	27.8 ±5.1	36.2 ±6.3
Total body fat percentage DXA (%)	22.1 ±6.2	27.8 ±6.7*	30.7 ±5.2	36.0 ±6.1*
ASM BIA (kg)	22.9 ±2.6	20.5 ±3.0	15.7 ±1.8	14.6 ±2.3
ASM DXA (kg)	22.2 ±2.6	19.8 ±2.8*	14.9 ±1.7	14.3 ±2.1*
ASMI BIA (kg/m^2)	7.68 ±0.54	7.44 ±0.73	6.07 ±0.48	6.11 ±0.70
ASMI DXA (kg/m^2)	7.47 ±0.68	7.21 ±0.83*	5.77 ±0.53	6.04 ±0.72*
Dominant hand grip (kg)	43.3 ±6.7	34.5 ±6.8	26.5 ±3.8	22.3 ±4.5
Gait speed (m/s)	1.61 ±0.28	1.27 ±0.26	1.49 ±0.26	1.22 ±0.26

Data are mean ± SD. BMI, body mass index; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.

**A total of 10% of the older subjects were selected randomly to receive a measurement of muscle mass using the DXA method (n = 147 for men and n = 143 for women).*

and specificity greater than 0.8. Sensitivity, specificity, positive and negative predictive values, area under the curve (AUC), accuracy between existing guidelines, and our proposed cutoffs were calculated.

RESULTS

Participants' Characteristics

A total of 2,821 (1,398 men and 1,423 women) older adults aged ≥60 years and 409 (205 men and 204 women) young adults aged 25–34 years were included in this study, and their characteristics are presented by gender (**Table 1**).

As shown in **Table 2**, by using existing definitions (7–12), the prevalence of sarcopenia in older adults ranged from 0 to 27.0% in men and 0 to 25.2% in women. The prevalence of low muscle mass using DXA varied from 0.7 to 51.0% in men and 16.1 to 30.1% in women, while the prevalence of low muscle mass using BIA was from 26.2 to 97.4% in men and 18.1 to 68.0% in women. Low handgrip ranged from 9.5 to 34% in men and 7.3 to 30.1% in women. The prevalence of low gait speed varied from 2.6 to 17.5% in men and 3.5 to 18.3% in women. Comparing the BIA and DXA, the prevalence of low muscle mass was significantly different in men in all the guidelines but significantly different in women only for the EWGSOP and AWGS cutoffs (**Supplementary Table S2**). Furthermore, the prevalence of low muscle mass was expectedly higher using the cutoffs defined in EWGSOP compared with other defined guidelines since it used higher thresholds for low handgrip and low ASMI using DXA and BIA.

Identifying Optimal BIA Cutoffs for Low ASMI According to DXA Cutoffs

Dual-energy X-ray absorptiometry results showed (**Supplementary Table S1**) that the three cutoff points used for men were 6.10 kg/m^2 (ASMI-2 SD), 6.79 kg/m^2 (ASMI-1 SD), and 6.53 kg/m^2 (ASMI 20) and in women, the cutoff points were 4.71, 5.24, and 5.40 kg/m^2, respectively. Accordingly, the proportions of low ASMI in older subjects were 10.2% (ASMI-2 SD), 30.6% (ASMI-1 SD), and 21.1% (ASMI 20) in men and 2.8% (ASMI-2 SD), 14.0% (ASMI-1 SD), and 20.3% (ASMI 20) in women. The prevalence defined by ASMI-2 SD and ASMI-1 SD showed a significant gender difference ($p = 0.01$ and $p = 0.007$, respectively). Consequently, 6.53 kg/m^2 in men and 5.40 kg/m^2 in women were selected as the best cutoff values, respectively, determined by the 20th percentiles of the older adults' group as shown in **Table 3**.

Dual-energy X-ray absorptiometry results were considered as criteria to validate BIA measurements. The ASMI measured by BIA showed strong correlations with the measurements by DXA in both men and women ($r = 0.77$ and $p < 0.001$ in men; $r = 0.79$ and $p < 0.001$ in women; **Figures 1A,B**). Bland–Altman plot (**Supplementary Figure S1**) shows good agreement between the BIA and DXA measurements of ASMI. Additionally, the concordance correlation coefficient also showed substantial agreement between BIA and DXA on ASMI for males, 95% CI, 0.83–0.94; for females, 95% CI, 0.90–0.97. The AUCs of the low muscle mass index measured by BIA were 0.89 (95% CI, 0.97–0.98) and 0.93 (95% CI, 0.94–0.97) in men and women, respectively. The low ASMI value using BIA that best predicts the low ASMI using DXA (<6.53 and <5.40

TABLE 2 | Sarcopenia prevalence based on different existing definitions.

Existing definitions of sarcopenia	Prevalence (DXA cohort, *n* = 290)			Prevalence (BIA cohort, *n* = 2,821)		
	Male (*n* = 147)	Female (*n* = 143)	*p* value	Male (*n* = 1,398)	Female (*n* = 1,423)	*p* value
AWGS (11)	9 (6.1)	7 (4.9)	0.65	84 (6.0)	123 (8.6)	0.007
Low muscle mass	62 (42.2)	37 (25.9)	0.003	366 (26.2)	391 (27.5)	0.44
Low hand grip	14 (9.5)	26 (18.2)	0.03	141 (10.1)	226 (15.9)	<0.001
Low gait speed	4 (2.7)	5 (3.5)	0.70	38 (2.7)	60 (4.2)	0.03
IWGS (7)	12 (8.2)	5 (3.5)	0.09	93 (6.7)	102 (7.2)	0.59
Low muscle mass	75 (51.0)	43 (30.1)	<0.001	538 (38.5)	369 (25.9)	<0.001
Low hand grip	.	.	.	.	.	.
Low gait speed	20 (13.6)	20 (14.0)	0.93	189 (13.5)	260 (18.3)	0.001
EWGSOP (8)	33 (22.4)	14 (9.8)	0.003	378 (27.0)	359 (25.2)	0.27
Low muscle mass	75 (51.0)	43 (30.1)	<0.001	1362 (97.4)	968 (68.0)	<0.0001
Low hand grip	50 (34.0)	43 (30.1)	0.47	371 (26.5)	425 (29.9)	0.05
Low gait speed	4 (2.7)	5 (3.5)	0.70	37 (2.6)	55 (3.9)	0.07
FNIH (9)	2 (1.4)	0 (0)	0.16	11 (0.8)	12 (0.8)	0.87
Low muscle mass	73 (49.7)	23 (16.1)	<0.001	490 (35.1)	257 (18.1)	<0.001
Low hand grip	14 (9.5)	11 (7.7)	0.58	141 (10.1)	104 (7.3)	0.01
Low gait speed	4 (2.7)	5 (3.5)	0.70	38 (2.7)	60 (4.2)	0.03
AWGS (32)	23 (15.6)	7 (4.9)	0.003	155 (11.1)	171 (12.0)	0.44
Low muscle mass	62 (42.2)	29 (20.3)	<0.0001	366 (26.2)	391 (27.5)	0.44
Low hand grip	35 (23.8)	26 (18.2)	0.24	189 (13.5)	260 (18.3)	<0.001
Low gait speed	20 (13.6)	20 (14.0)	0.93	244 (17.5)	226 (15.9)	0.26
EWGSOP2 (10)	0 (0.0)	2 (1.4)	0.15	93 (6.7)	44 (3.1)	<0.001
Low muscle mass	1 (0.7)	37 (25.9)	<0.001	366 (26.2)	262 (18.4)	<0.001
Low hand grip	22 (15.0)	11 (7.7)	0.05	180 (12.9)	104 (7.3)	<0.001
Low gait speed	4 (2.7)	5 (3.5)	0.70	38 (2.7)	60 (4.2)	0.03

Data represented n (%). DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; AWGS, Asia Working Group of Sarcopenia; IWGS, International working group on sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institute of Health.

kg/m^2 in men and women, respectively) was <7.05 kg/m^2 in men (sensitivity: 0.81, 95% CI: 0.63–0.93; specificity: 0.80, 95% CI: 0.72–0.87) and <5.85 kg/m^2 in women (sensitivity: 0.90, 95% CI: 0.73–0.98; specificity: 0.81, 95% CI: 0.72–0.87) (**Figures 2A,B**).

Cutoffs of Muscle Strength and Gait Speed

Percentiles of muscle mass, handgrip strength, and gait speed are given in **Table 3**. Following the AMI rules measured by DXA, the lowest 20th percentile value of 28.5 and 18.6 kg in men and women, respectively, from the older adults' group was selected as cutoffs for low handgrip strength. In addition, 1.05 and 1.01 m/s in men and women were, respectively, selected for low gait speed based on the lowest 20% of the older adults' group.

Based on the derived cutoffs, 14.2% of men and 15.7% of women in the older Chinese study population were classified to have sarcopenia (**Table 4**). The prevalence was 7.5 and 10.1% (60–69 years), 24.2 and 24.5% (70–79 years), and 43.6 and 62.5% (≥80 years) in men and women, respectively.

Comparison With Existing Guidelines

Sensitivity, specificity, negative predictive values, AUC, and accuracy were high between the proposed cutoffs derived in this study and the AWGS, IWGS, and EWGSOP2 guidelines, but lower relative to FNIH and EWGSOP. This may be due to the different low muscle mass measures used as follows: ASMI for our cutoffs, ASM/BMI for FNIH, the requirement to meet low muscle mass, low grip strength, and low gait speed with the FNIH, and the higher thresholds for EWGSOP. The low positive predictive values, as well as the lower values for women relative to men, were expected since our proposed cutoffs, and more so for women than men, tended to be higher than existing guidelines (**Table 5**). Cutoffs for sarcopenia and its components as defined by existing guidelines used in the comparisons are provided in **Supplementary Table S3**.

DISCUSSION

This study establishes cutoffs of grip strength, gait speed, and BIA-derived low muscle mass based on a large, gender- and

TABLE 3 | Percentiles for muscle mass, handgrip strength, and calf circumference parameters of the older reference population (n = 2,821).

Percentiles	Males (n = 1398)				Females (n = 1423)			
	ASMI-DEXA* (kg/m^2)	ASMI-BIA (kg/m^2)	Hand grip (kg)	Gait speed (m/s)	ASMI-DEXA* (kg/m^2)	ASMI-BIA (kg/m^2)	Hand grip (kg)	Gait speed (m/s)
5	6.00	6.29	23.9	0.89	4.93	5.02	15.0	0.83
10	6.10	6.57	25.9	0.96	5.03	5.28	16.6	0.91
15	6.37	6.72	27.5	1.01	5.28	5.42	17.7	0.97
20	6.53	6.88	28.5	1.05	5.40	5.55	18.6	1.01
25	6.59	6.97	29.7	1.1	5.46	5.66	19.3	1.04
30	6.76	7.07	30.7	1.14	5.66	5.76	20.0	1.08
35	6.88	7.16	31.8	1.16	5.77	5.86	20.6	1.11
40	6.98	7.26	32.6	1.2	5.86	5.94	21.2	1.14
45	7.06	7.33	33.5	1.22	6.00	6.03	21.8	1.17
50	7.20	7.43	34.3	1.26	6.10	6.09	22.3	1.19
55	7.31	7.51	35.2	1.29	6.15	6.18	22.9	1.23
60	7.40	7.60	36.1	1.32	6.25	6.27	23.4	1.26
65	7.50	7.71	37.1	1.35	6.33	6.38	24.0	1.30
70	7.55	7.81	38.1	1.39	6.43	6.46	24.7	1.34
75	7.66	7.93	39	1.42	6.57	6.54	25.2	1.38
80	7.79	8.04	40.3	1.45	6.67	6.66	26.2	1.43
85	7.99	8.19	41.8	1.52	6.80	6.77	27.1	1.47
90	8.29	8.35	43.3	1.59	6.98	6.95	28.1	1.55
95	8.73	8.64	46	1.69	7.10	7.20	29.5	1.68

ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.
**A total of 10% of the older subjects were selected randomly to receive a measurement of muscle mass using the DXA method (n = 147 for men and n = 143 for women).*

geography-diverse Chinese study population. We particularly recruited equal numbers of male and female participants in their early adult years in order to capture peak skeletal muscle mass in both genders since muscle mass gradually declined with aging. We also specifically chose Beijing and Shanghai as study sites since they were two of the largest cities in China representing distinguishable diets and lifestyles in Northern and Eastern China. Our results confirm that BIA provides a valid and easy estimation of skeletal muscle mass using DEXA as a reference standard. The findings of our study contribute new evidence to a better understanding of muscle quantity, muscle function, and performance in healthy young Chinese adults and older Chinese adults. These values can be potentially used for assessing sarcopenia in older Chinese people in an epidemiological and clinical setting.

Obvious differences exist in the cutoffs among the proposed of this study and the AWGS, EWGSOP, EWGSOP2, IWGS, and FNIH recommendations. The cutoff values derived from the Caucasian Panel criteria based on different racial reference populations are inapplicable to the Chinese population. Besides, data from the Chinese population residing in mainland China are lacking in the AWGS. In this large cohort, the findings first demonstrated how existing sarcopenia definitions impact the proportion of sarcopenia in the Chinese older population. With the exception of EWGSOP, the prevalence of sarcopenia in the older study population ranged from 0.0 to 15.6% in men and 0.0 to 12.0% in women with significant gender differences. It is lower than most of the reported prevalence ranging from 10 to 40% (2, 22, 26–30). It is worth noting that existing sarcopenia definitions produced underestimated prevalence of sarcopenia. It decreases awareness of sarcopenia and its risk in China. Underestimating sarcopenia in older Chinese adults is not conducive to early prevention.

Older and younger adults show differences in weight, height, muscle mass, muscle strength, and physical performance due to the aging process, which was also observed in our study (**Table 1**) but excluded the ASMI in women. The mean of ASMI is similar or even higher in older female adults than in the young group in this study (ASMI BIA: 6.07 kg/m^2 in young women vs. 6.11 kg/m^2 in older women; ASMI DXA: 5.77 kg/m^2 in young women vs. 6.04 kg/m^2 in older women). That is the reason why 4.71 kg/m^2 (ASMI-2 SD) and 5.24 kg/m^2 (ASMI-1 SD) in young adults are even lower than 5.40 kg/m^2 (ASMI 20) in the older women in this study. Consequently, this produced an unacceptably low proportion of low muscle mass in older women (2.8 and 14.0% for ASMI-2 SD and ASMI-1 SD, respectively). Interestingly, other studies in Asian cohorts reported a similar result (33). This may be due to Asian women in their 20 s and 30 s tending to prefer a slim body with a focus on diet restriction in the latest decades, which harms muscle development. Besides, the prevalence defined by ASMI-2 SD and ASMI-1 SD showed

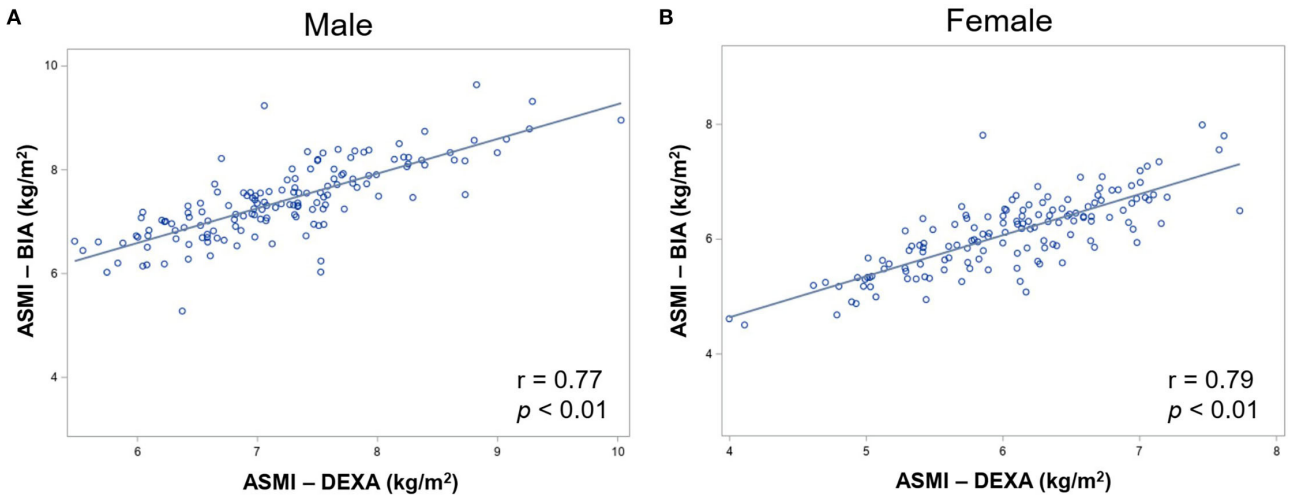

FIGURE 1 | Correlation between DXA and BIA measured ASM in **(A)** male and **(B)** female participants. DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; ASMI, appendicular skeletal muscle mass.

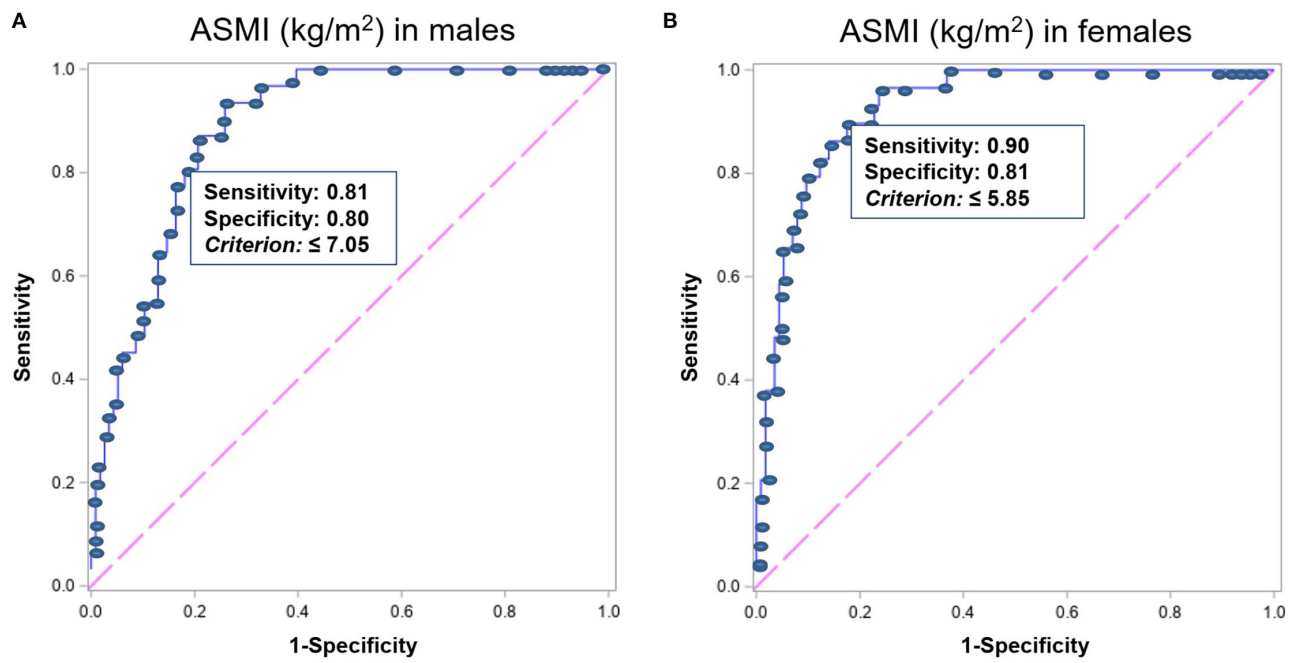

FIGURE 2 | The ROC analysis results of ASMI measured by BIA for predicting ASMI measured by DXA <6.53 and 5.40 kg/m^2 in men and women, respectively, indicating the ASMI value of ideal highest sensitivity and specificity in **(A)** men (n = 1,398) and **(B)** women (n = 1,423). ROC, receiver operating characteristics; ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.

significant gender difference (p = 0.01 and p = 0.007, respectively). Therefore, the lowest 20% of the older group is the optimal standard cutoff value for DXA (6.53 and 5.40 kg/m^2 in men and women, respectively) to obtain a meaningful proportion of low muscle mass without significant gender difference.

Dual-energy X-ray absorptiometry is slowly becoming more available even if it remains too costly and requires expertise in performing measurements. The application of the BIA method in clinical practice used to be criticized due to its large inaccuracy resulting from analysis assumptions related to body shapes and the distribution of current density (34). However, recent

TABLE 4 | Prevalence of low muscle mass, low hand strength, low gait speed, and sarcopenia by gender-based on proposed cutoffs.

Parameters	Proposed cutoffs	Overall	60 y–69 y	70 y–79 y	≥80 y
Male		**N = 1,398**	**N=904**	**N = 439**	**N = 55**
① Low muscle mass (BIA), kg/m	7.05	407 (29.1)	209 (23.1)	169 (38.5)	29 (52.7)
② Low hand grip, kg	28.5	278 (19.9)	102 (11.3)	141 (32.1)	35 (63.6)
③ Low gait speed, m/s	1.05	258 (18.5)	116 (12.8)	116 (26.4)	26 (47.2)
Sarcopenia	① + ② or ① + ③	198 (14.2)	68 (7.5)	106 (24.2)	24 (43.6)
Female		***N* = 1,423**	***N* = 979**	***N* = 404**	***N* = 40**
① Low muscle mass (BIA), kg/m	5.85	485 (34.1)	279 (28.5)	180 (44.6)	26 (65.0)
② Low hand grip, kg	18.6	283 (19.9)	135 (13.8)	118 (29.2)	30 (75.0)
③ Low gait speed, m/s	1.01	276 (19.4)	137 (14.0)	112 (27.7)	27 (67.5)
Sarcopenia	① + ② or ① + ③	223 (15.7)	99 (10.1)	99 (24.5)	25 (62.5)

Values were n (%). BIA, bioelectrical impedance analysis.

TABLE 5 | Sensitivity, specificity, positive and negative predictive values, area under the curve (AUC), and accuracy between the proposed cutoffs relative to existing guidelines.

Reference guideline	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	Area under curve
AWGS (11)						
Male	100	91.3	41.9	100	91.8	0.9215
Female	100	72.4	25.5	100	74.8	0.9209
AWGS (32)						
Male	100	96.5	78.3	100	96.9	0.9357
Female	100	75.2	35.5	100	78.1	0.9317
IWGS (7)						
Male	84.9	90.9	39.9	98.8	90.5	0.8711
Female	100	71.2	21.2	100	73.3	0.9140
EWGSOP (8)						
Male	42.3	96.3	80.8	81.8	81.7	0.6901
Female	65.5	76.8	48.8	86.8	73.9	0.8072
EWGSOP2 (10)						
Male	100	92.0	47.0	100	92.5	0.9267
Female	100	68.2	9.1	100	69.2	0.9400
FNIH (9)						
Male	54.5	86.2	3.0	99.6	85.9	0.6914
Female	72.7	66.4	1.7	99.7	66.5	0.7641

Data represented %. AWGS, Asia Working Group on Sarcopenia; IWGS, International working group on sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institute of Health.

advances in technology facilitate the development of new BIA devices with improved accuracy and high precision (35). The findings of this study showed excellent agreement between BIA and DXA methods in muscle mass measurement, though a small systematic bias existed. The reported systematic bias in this study is within the range of previously published data (0.1–2.1 kg) (18, 36, 37). Considering that the DXA used in estimating body composition is the reference method, the low ASMI threshold of the BIA using the ROC analysis represented the cutoff value of <6.53 and 5.40 kg/m^2 in men and women, respectively, to identify the ASMI of the participants measured by BIA. The data in this study indicated that the low ASMI measured by BIA cut-point thresholds are 7.05 kg/m^2 (sensitivity, 0.81; specificity, 0.80) in men and 5.85 kg/m^2 (sensitivity, 0.90; specificity, 0.81) in women. This finding follows the data of sarcopenia assessment in Korea (38), which is very important for assessing and managing sarcopenia in China. Among three components, the methods to determine low muscle mass using DXA show limitations in application in primary care settings. Therefore, our study replaces DXA with BIA, an easier but accurate measure, which will enhance the screening of sarcopenia in the general population, to achieve attention and early intervention. We proposed the cutoffs, 7.05 kg/m^2 for men, and 5.85 kg/m^2 for women, showing high sensitivity of over 80% to identify older people with reduced muscle mass.

The cutoff of muscle strength for IWGS, FNIH, EWGSOP, and EWGSOP2 (7–10) showed a significant difference in low muscle strength proportion between men and women. In this study, the cutoff for handgrip strength was found to be 28.5 and 18.6 kg in men and women, using the sex-specific lowest 20% quintile points of the handgrip strength in the older study population, respectively. It is the optimal cutoff of muscle strength for older adults in China. The finding is similar to the cutoff of low handgrip strength (28.8 and 18.2 kg for men and women, respectively) in sarcopenia definition in Japan (39). Of note, 0.8 m/s is the cutoff for low gait speed used in EWGSOP, FNIH, and AWGS (8, 9, 11). But it showed an extremely low proportion (2.7–4.2%) of low gait speed without clinical relevance since 0.8 m/s is slower than the lowest 5% gait speed in the older male and female study population (**Table 2**). Therefore, the same rule using the sex-specific lowest 20% in the older study group was followed to define the thresholds for gait speed. The corresponding thresholds for gait speed were 1.05 and 1.01 m/s for men and women, respectively. By using the new cutoff thresholds of three components set up in this study, the overall proportion of sarcopenia was 14.2 and 15.7% for men and women, respectively. This new threshold to be used for assessing sarcopenia in older Chinese people is more optimal than other existing sarcopenia definitions.

This study has several strengths. First, this study had a relatively large sample size of more than 2,800 and 400 older and young Chinese people, respectively. Both the older and young study groups have sample sizes higher than or comparable with most of the other reference population data in the literature (21, 24, 26, 32, 39, 40). Second, this study selected three cities (i.e., Beijing, Shanghai, and Chengdu) according to the characteristics of the typical life and dietary pattern to ensure the representativeness of the study population. Finally, by using DXA as the gold standard technology for the assessment of skeletal muscle, this study proposed cutoff thresholds for BIA as a good portable alternative measure to DXA. This will improve the application of screening and awareness of sarcopenia in the older Chinese population. However, it also has several limitations. The first limitation of this study is that the study population did not include the rural population. Thus, care should be exercised when extrapolating these cutoffs to different populations. Second, although we chose residents of three representative cities in mainland China as the study population for this study, it has to be acknowledged that there may be some potential selection bias in the sample, so in future studies, we will further develop a variety of new joint surveys to increase the generalizability and persuasiveness of the findings. The third limitation is we did not design a longitudinal follow-up of the cohort to reveal the changes in muscle strength, muscle mass, and physical performance over time.

In conclusion, this study proposed the sex-specific cutoff for three components of sarcopenia. The 7.05 kg/m^2 in men and 5.85 kg/m^2 in women were selected as the optimal cutoffs of BIA for low ASMI. The 28.5 kg and 1.05 m/s for men and 18.6 kg and 1.01 m/s for women were determined as the optimal cutoffs for handgrip strength and gait speed, respectively. These optimal cutoffs will enhance practicability for screening sarcopenia in primary care and clinical settings.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WC, SG, and BD contributed to the conception and design of the research. WC, SG, BD, XF, HW, SH, XS, WS, AM, TL, and HL contributed to the acquisition of the data. QD, VP, GB, and MY contributed to the analysis and interpretation of the data. QD and SG drafted the manuscript. QD substantially revised the submitted version. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Journal of Cachexia, Sarcopenia and Muscle: update 2017 were complied (41).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.853323/full#supplementary-material

Supplementary Figure S1 | Bland–Altman plot of ASMI between BIA and DXA. ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.

Supplementary Table S1 | Cutoff values and proportions of flow muscle mass based on DXA.

Supplementary Table S2 | Comparison of prevalence's between BIA and DXA.

Supplementary Table S3 | Cutoff's for sarcopenia based on different guidelines.

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Conflict of Interest: VP and MY are employees of Cognizant Technology Solutions, which provides statistical services to Abbott.

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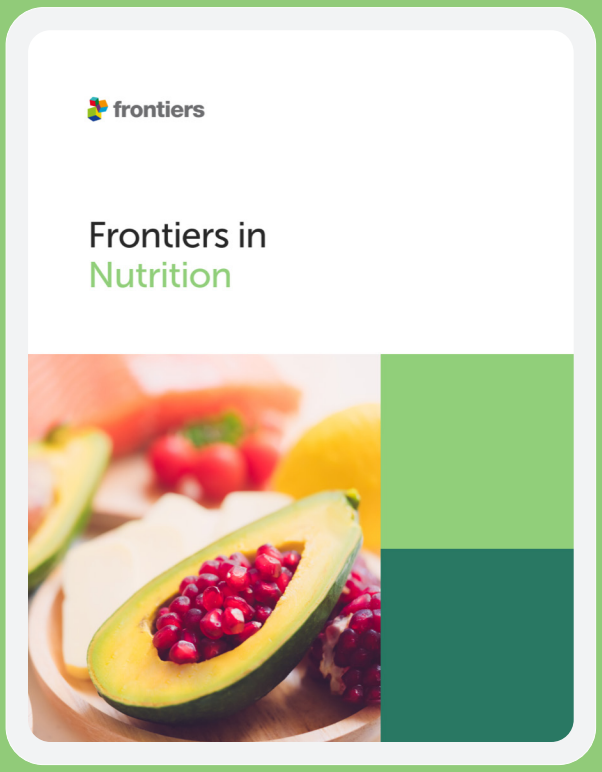

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