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ALM adjusted by BMI or weight predicts adverse health outcomes in middle-aged and elderly patients with type 2 diabetes

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The role of skeletal muscle in the prognosis of patients with Type 2 Diabetes Mellitus (T2DM) remains unclear. This study aimed to systematically evaluate the impact of different muscle-mass adjustment standards on adverse health outcomes in middle-aged and elderly T2DM patients. Retrospective cohort study. A total of 1,818 T2DM patients aged 50 years or older were included in this study. The cohort comprised 45.7% females, with a median age of 63 years. Variables closely correlated with total lean mass (TLM) and appendicular lean mass (ALM) were selected as adjustment indicators. The primary composite endpoints were all-cause mortality, cardiovascular disease (CVD), and fragility fractures. Cox proportional hazards models were used to estimate the risk associated with each indicator, and phenotypic characteristics of high-risk patients were evaluated. During a median follow-up of 63 months, 436 patients reached the primary endpoint. ALM/BMI and ALM/weight were negatively correlated with adverse outcomes in both sexes, even after adjusting for confounding factors (males: ALM/BMI (hazard ratio [HR] = 0.998, 95% confidence interval [CI] = 0.996–0.999, *P* = 0.005) and ALM/weight (HR = 0.924, 95% CI = 0.864–0.987, *P* = 0.020); females: ALM/BMI (HR = 0.998, 95% CI = 0.996-1.000, *P* = 0.030) and ALM/weight (HR = 0.917, 95% CI = 0.860–0.978, *P* = 0.008), respectively). Individuals with lower ALM/BMI and ALM/weight have poorer metabolic status, greater fat accumulation, more complications, and a lower muscle-to-fat ratio. Our findings demonstrate that both ALM/BMI and ALM/weight can predict adverse health outcomes, suggesting their potential as practical, clinically relevant markers for sarcopenia in T2DM.

Keywords Type 2 diabetes mellitus, Sarcopenia, Appendicular lean mass index, Mortality, Cardiovascular disease, Fragility fracture

Metabolic flexibility, a crucial mechanism for rapidly adapting to environmental shifts, usually requires coordinated interactions among multiple organs and tissues[1]. Unfortunately, in recent years, with changes in lifestyle, the extension of life expectancy, and increased exposure to endocrine disruptors, the plasticity of metabolism has gradually diminished, leading to a massive surge in chronic degenerative metabolic diseases, including type 2 diabetes mellitus (T2DM), obesity, sarcopenia, atherosclerotic cardiovascular disease (ASCVD), and osteoporosis[2].While the harmful effects of excessive obesity have received considerable attention, the potential protective role of higher muscle mass in T2DM patients has not been adequately studied. Research indicates that relatively higher muscle mass during middle age can prevent the development of T2DM[3], whereas low appendicular lean mass (ALM) is associated with various adverse health outcomes, such as decreased grip strength, slowed walking speed, and increased fracture risk[4,5].

There is ongoing debate regarding the methods used to assess ALM. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO)[6] suggest defining sarcopenia in sarcopenic obesity (SO) as "a relative reduction in muscle mass, adjusted for body weight." Additionally, a study has found that diabetes patients have reduced lean mass and increased fat mass compared

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to non-diabetics[7], indicating that diabetes may increase the risk of SO. This risk has been consistently shown to be a strong and independent factor for frailty, comorbidities, and mortality in the general population, especially among older adults[8,9].Traditionally, ALM divided by height squared (ALM/height^2) has been the most widely used method to identify low muscle mass[10,11]. However, this approach fails to account for body weight, potentially leading to the misclassification of individuals with low "muscle percentage"[12–14]. In the context of T2DM, where SO is more prevalent, considering body weight when adjusting ALM becomes particularly important. In a cross-sectional study of a Taiwanese community population[15], ALM/weight was found to be more effective in illustrating the impact of aging on sarcopenia prevalence and in identifying individuals with SO compared to ALM/height^2.Preliminary research suggests that ALM/BMI may be more accurate than ALM/height^2 in obese, prediabetic, or diabetic patients[16,17]. Moreover, subsequent studies have demonstrated that a higher ALM/BMI is correlated with a reduced risk of T2DM among middle-aged adults[3] and a lower risk of metabolic syndrome in individuals 20 years of age or older in South Korea[18]. Therefore, the optimal ALM adjustment method for accurately identifying individuals at greater risk for subsequent functional limitations and unfavorable clinical outcomes in T2DM remains uncertain.

To select the optimal ALM adjustment method for accurately identifying individuals with T2DM, we comprehensively considered relevant variables.Given that absolute muscle mass is closely related to body size and composition, the selection of ALM adjustment variables was guided by the use of relative muscle mass to define sarcopenia. Commonly used body - size indicators include height, weight, BMI, and body surface area (BSA). Considering muscle mass is also influenced by fat mass, we included body composition variables such as body fat mass (BFM), percent body fat (PBF), appendicular fat mass (AFM), and visceral fat mass (VFM). Considering the performance of ALM/BMI or ALM/weight in other populations, this study aims to explore whether relative ALM measures like ALM/BMI or ALM/weight are associated with a lower risk of adverse health outcomes in middle-aged and older T2DM patients. We hypothesize that higher ALM/BMI and ALM/weight are linked to a reduced risk of adverse health outcomes in these patients and that these two measures are the most suitable for defining sarcopenia in this population.

Methods

Study design and population

This study is based on our own established Ageing and Body Composition of Diabetes (ABCD) cohort, a single-center, retrospective cohort specifically designed to explore the impact of body composition on adverse outcomes in patients with T2DM. The study utilized electronic medical records (EMRs) from the Department of Endocrinology at the First Affiliated Hospital of Chongqing Medical University, covering the period from January 2015 to August 2019. The EMR system includes demographic information, clinical diagnoses, laboratory test results, medication histories, and imaging findings. All aspects of the study, including data collection, follow-up, data cleaning, statistical analysis, and interpretation of results, were independently completed by the authors, with rigorous quality control measures in place. This ensures the completeness and authenticity of the research data.

The study included individuals aged 50 years or older who met the diagnostic criteria for T2DM established by the World Health Organization in 1999. Initially, a total of 5,971 patients were enrolled in the study, as illustrated in Fig. S1. The exclusion criteria were as follows: (1) not undergoing whole-body dual-energy X-ray absorptiometry (DXA); (2) having preexisting medical conditions or medication usage that could influence body composition, such as malignant tumors, other endocrine diseases (e.g., dysfunction from thyroid, parathyroid, pituitary or adrenal glands), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus), organ failure (moderate to severe heart failure, chronic lung disease and liver insufficiency, chronic kidney disease with an estimated glomerular filtration rate (eGFR) $\leq$ 45 ml/min/1.73 m^2), gastrointestinal disorders (inflammatory bowel disease, malabsorption), neuromuscular disorders (e.g., muscular dystrophy, myasthenia), history of bariatric surgery, depression, other psychiatric disorders, or use of steroids and psychotropic medications or bisphosphonate; (3) having acute medical disorders such as severe infections, acute diabetes complications, pregnancy, trauma, surgery, or other stressful situations; (4) having factors that could affect the interpretation of the DXA results, such as edema, amputation or body part loss, or the presence of artificial joints or implants; (5) declining to participate in the study; (6) having incomplete clinical data; and (7) being lost to follow-up. Ultimately, 1,818 eligible participants were included in the current analysis. The analyses were conducted for the total population and separately for males and females.

Body composition assessment

Total and appendicular lean mass were estimated using DXA with an identical Hologic scanner (Discovery A, S/N 87352, Hologic, Bedford, USA), and all measurements were taken at baseline. Quality control of the DXA scans in this study is described in detail in the Supplementary material, Methods. We considered 8 different scaling factors to adjust Total Lean Mass (TLM) and ALM: height^2, weight, BMI, BSA, BFM, PBF, AFM, and VFM.

BMI was calculated by dividing weight (in kg) by the square of height (in m^2). The BSA was calculated using the Mosteller formula[19]: BSA (in m^2) = [weight (in kg) $\times$ height (in cm)/3600]^{½}. ALM or AFM was determined by summing the lean or adipose tissue mass of all four extremities. The appendicular muscle-to-fat ratio (MFR) was defined as the ratio of ALM to AFM. Both TLM/BMI and ALM/BMI are expressed in units of g/BMI.

Measurements of covariates and biomarkers

Our research team members underwent unified training to ensure consistency and accuracy in baseline data collection, which formed the foundation for all subsequent analyses and evaluations.These data included key demographic characteristics such as sex, age, current smoking or drinking status, and duration of diabetes.

Standardized procedures were used for the measurement of blood pressure (both systolic and diastolic) and anthropometric variables such as height and weight. Laboratory evaluation focused on metabolic traits, including fasting plasma glucose, hemoglobin A1c (HbA1c), and lipid profile (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides). Additionally, renal metabolic panel assessments, which included serum uric acid, urinary albumin-to-creatinine ratio (uACR) and eGFR, along with nutritional and inflammatory markers like albumin, prealbumin, hemoglobin, and high-sensitivity C-reactive protein(hsCRP) levels, were conducted. This study also examined clinical characteristics, including diabetes-related complications (such as retinopathy, nephropathy, peripheral neuropathy, carotid atherosclerosis, and peripheral artery disease), common comorbidities (hypertension, coronary heart disease, stroke, and prior CVDs or fractures), and corresponding drug usage. The severity of diabetic complications was evaluated using the Diabetes Complications Severity Index (DCSI).

The eGFR was calculated using the formula developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The DCSI, a 13-point scale developed by Young BA et al.[20], better predicts the risk of adverse outcomes in diabetes patients based on automated diagnostic, pharmacy, and laboratory data.

Outcome ascertainment

Patients in the study were diligently tracked and monitored using various methods, including in-person interviews, meticulous review of medical records, and thorough telephone interviews. Additionally, unless an event occurred prior to the follow-up cutoff, all participants were contacted via telephone, ensuring thorough data collection and patient monitoring. The follow-up data focuses solely on new health events after the initial visit, ensuring it is distinct from baseline data. Medical records were reviewed on an irregular basis, being checked as needed. Follow-up began at the time of patient recruitment and continued until the first occurrence of any primary endpoint (CVD, fragility fracture, or all-cause mortality) or until June 30, 2022, whichever came first. Furthermore, in the sub-analysis, the secondary endpoints were considered as components of the composite primary endpoint, a practice based on previous studies[21]. This approach not only comprehensively evaluates the mechanical and metabolic functions of muscle mass but also increases statistical power by expanding the number of cases.

The determination of mortality status relied on the electronic medical record system of the First Affiliated Hospital of Chongqing Medical University, death certificates from specialist physicians, and follow-up phone calls with family members for confirmation. During interviews with the study participants, we primarily sought information on their general health status, with particular emphasis on whether they had experienced any CVDs or fractures as specified in the manuscript. CVDs encompass a range of conditions, including fatal cardiovascular/cerebrovascular events, nonfatal myocardial infarction or unstable angina, procedures involving the revascularization of coronary or peripheral arteries, nonfatal ischemic or hemorrhagic stroke, and transient ischemic attack. Additionally, we inquired about the occurrence of acute events accompanied by relevant symptoms and the availability of diagnostic evidence from specialist physicians or imaging reports. Furthermore, we asked about the treatments received and the methods employed. Notably, we excluded cases where CVDs were solely diagnosed based on imaging without symptomatic evidence. We also excluded pathological fractures, traumatic fractures, or fractures in specific anatomical regions (e.g., skull, hand, finger, foot, toe).

Statistical analysis

Continuous quantitative data are presented as the means ± standard deviations (SDs) or medians with interquartile ranges (IQRs) in accordance with the results of the Shapiro–Wilk normality test. Categorical data are summarized as numbers and frequencies (%). Comparative analyses between the two groups were conducted using independent Student's t tests, nonparametric tests, or chi-square tests, as appropriate. To assess trends in population characteristics across the tertiles, the linear trend χ^2 test was used for categorical data, and either ANOVA or the Jonckheere-Terpstra test was used for quantitative data. Spearman correlation analysis was performed to examine the relationships between lean mass indices and specified scaling factors.

Cox proportional hazards models were utilized to calculate HRs and 95% CIs for the primary endpoints based on putative sarcopenia variables. Tests using Schoenfeld's residuals indicated no evidence of violation of the proportional hazards assumption. A single Cox model was employed, adjusting for age, smoking, alcohol consumption, and the severity of diabetes-related complications (including diabetes duration, HbA1c, and DCSI score). In the analysis of secondary endpoints, adjustments were made for other well-established CV risk factors, such as prior CVDs, LDL-C, and hypertension, to account for CVD endpoints. Similarly, additional adjustments were made for prior fractures and factors related to body composition, such as T scores ≤-2.5 for the lumbar spine, femoral neck, or total hip, in relation to fragility fracture endpoints. Receiver-operating characteristic (ROC) curve analysis was used to compare the predictive performance of ALM/weight and ALM/BMI in predicting the primary endpoints in patients with T2DM. The area under the ROC curve (AUC) was compared using the nonparametric Z test. A Venn diagram was also generated to evaluate the quantitative differences, both overlapping and nonoverlapping, between ALM/weight and ALM/BMI in relation to determining the primary endpoint.

A two-tailed p value less than 0.05 was considered to indicate statistical significance. The statistical analysis was conducted using IBM SPSS version 26.0 (SPSS Inc., Chicago, IL, USA), MedCalc® Statistical Software version 22.002 (MedCalc Software Ltd, Ostend, Belgium), and R (version 4.2.2; R Foundation).

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. K2023-402). All procedures were conducted in compliance with local legislation and institutional protocols. Due to the

retrospective nature of the study, the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University waived the need of obtaining informed consent.

Results

Participant characteristics

The baseline characteristics of the recruited participants are presented in Table S1. In the overall population, the subjects tended to be older (median age 63 years), overweight (median BMI 24.52 kg/m^2), and have a longer duration of diabetes (median duration 10 years), with a slight male predominance (54.3% vs. 45.7%).

As shown in Fig. 1, significant moderate to strong positive correlations were observed between ALM and scaling factors such as BSA, weight, BMI, height^2, body fat mass, and AFM in both males and females. Similar patterns were observed when analyzing the correlation between absolute TLM and these scaling factors (Fig. S2). To ensure robustness in the analysis, we selected scaling factors with a correlation coefficient of 0.40 or greater for both males and females. Consequently, the percentages of body fat mass and VFM did not meet the criteria and were excluded from subsequent analysis.

Association of ALM/BMI and ALM/weight with adverse health outcomes

To better illustrate the time-to-event data, we have plotted the Kaplan-Meier survival curve, which effectively depicts the cumulative incidence of the primary endpoints (CVD, fragility fracture, or all cause mortality) over time, starting from the recruitment date and excluding any baseline events (Fig. S3). During a median follow-up period of 63 months (interquartile range, 51 to 74 months), a total of 436 subjects (24.0%) experienced the composite primary endpoints, which consisted of 103 cases of all-cause death (23.6%), 277 cases of CVD (63.5%), and 101 cases of fragility fracture (23.2%). Notably, the incidence of primary endpoints was greater in

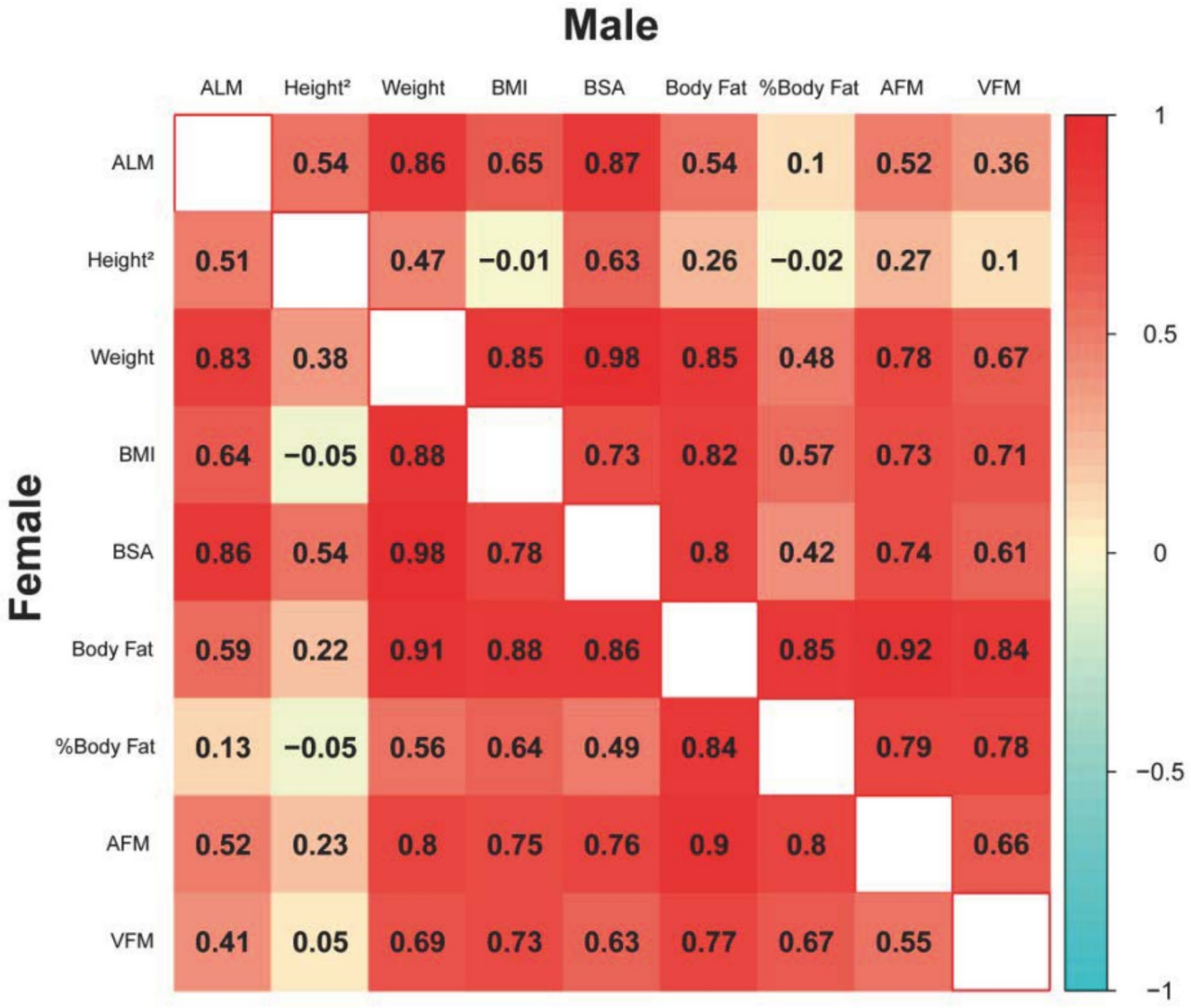

Fig. 1. Correlations between appendicular lean mass and different scaling factors. ALM, appendicular lean mass; BMI, body mass index; BSA, body surface area; AFM, appendicular fat mass; VFM, visceral fat mass.

females than in males (27.4% vs. 21.1%, $P = 0.002$). This difference stemmed primarily from the significantly greater incidence of fragility fractures among females than among males (9.6% vs. 2.1%, $P < 0.001$). However, no statistically significant difference was observed between males and females in terms of the incidence of all-cause death or CVD (6.0% vs. 5.3% and 15.6% vs. 14.8%, respectively, $P > 0.05$).

The analysis initially examined the association between TLM-based sarcopenia variables and composite primary endpoints (CVD, fragility fracture, or all cause mortality) but found no consistent results (Fig. S4), leading to a subsequent focus on the relationship between ALM and composite primary endpoints (CVD, fragility fracture, or all cause mortality). The results are shown in Fig. 2. Among males, three out of the six potential sarcopenia indicators based on ALM demonstrated significant negative associations with the prognosis, even after adjusting the Cox model for demographic and diabetes-specific factors. These indicators included ALM/BMI (HR = 0.998, 95% CI 0.996–0.999, $P = 0.005$), ALM/weight% (HR = 0.924, 95% CI 0.864–0.987, $P = 0.020$) and ALM/BSA (HR = 0.813, 95% CI 0.687–0.963, $P = 0.016$). In females, four out of the six potential sarcopenia indicators based on ALM exhibited significant associations with the prognosis. These indicators included ALM/BMI (HR = 0.998, 95% CI 0.996-1.000, $P = 0.030$), ALM/weight% (HR = 0.917, 95% CI 0.860–0.978, $P = 0.008$), ALM/total body fat mass (HR = 0.319, 95% CI 0.125–0.814, $P = 0.017$), and ALM/AFM (HR = 0.728, 95% CI 0.537–0.986, $P = 0.041$).These findings suggest that individuals with lower ALM adjusted for BMI or weight are more likely to experience incident primary endpoints (CVD, fragility fracture, or all cause mortality) in both

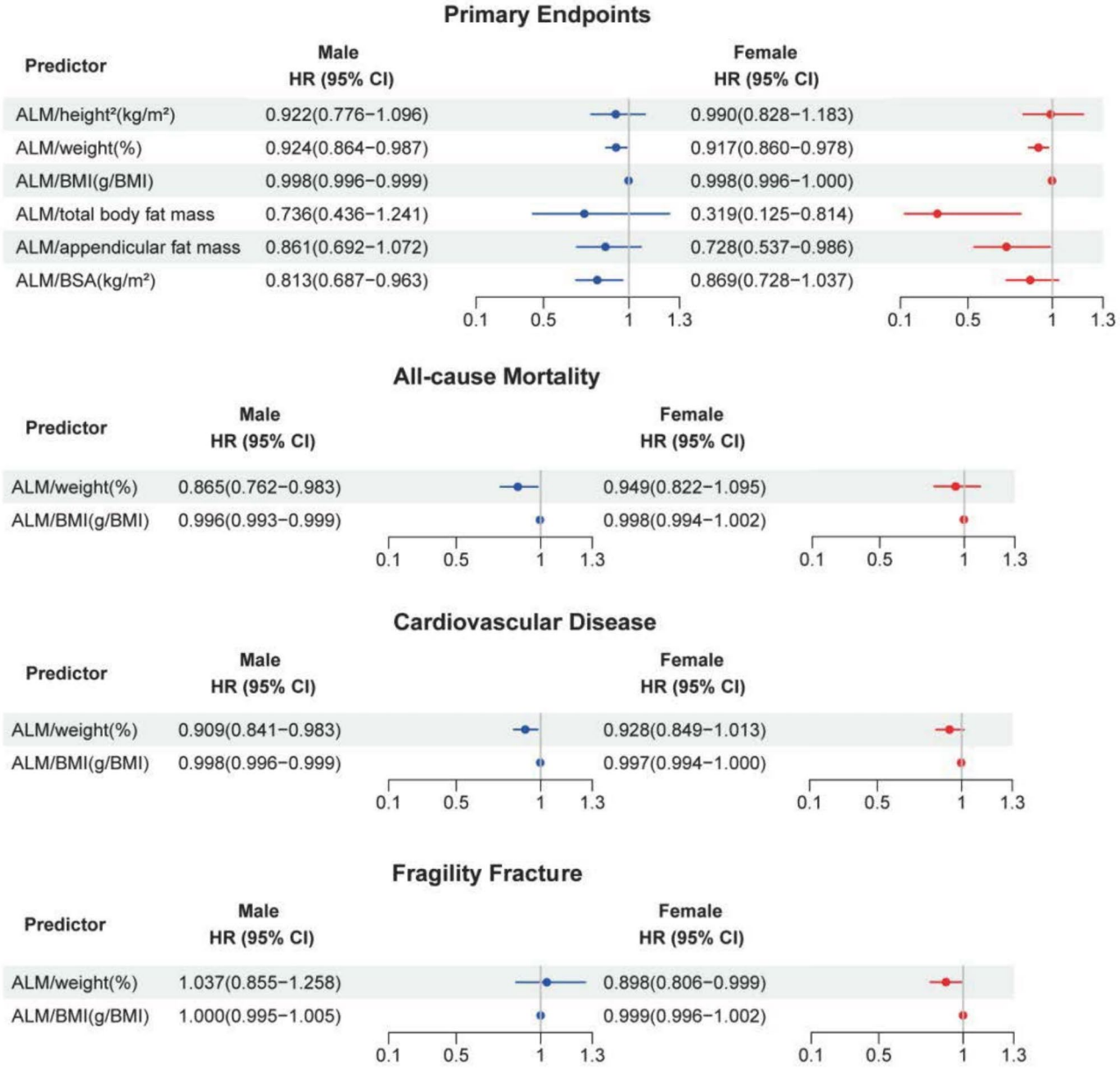

Fig. 2. Cox regression analysis was used to assess the association (HR, 95% CI) between putative sarcopenia variables and adverse outcomes in males and females.

	Male (n = 987)			Female (n = 831)		
	ALM/weight%	ALM/BMI (g/BMI)	*P*	ALM/weight%	ALM/BMI (g/BMI)	*P*
AUC (95%CI)	0.585 (0.554–0.616)	0.605 (0.574–0.636)	0.207	0.571 (0.536–0.605)	0.574 (0.539–0.608)	0.826
P value	< 0.001*	< 0.001*		0.001*	< 0.001*	
Youden index	0.1456	0.1660		0.1465	0.1306	
Cut-off value	≤ 29.18	≤ 820.34		≤ 24.02	≤ 594.71	
Sensitivity (%)	61.54	69.23		60.09	71.93	
Specificity (%)	53.02	47.37		54.56	41.13	
PPV (%)	25.91	25.99		33.17	31.47	
NPV (%)	83.77	85.22		78.15	79.23	
LR+	1.31	1.32		1.31	1.21	
LR-	0.73	0.65		0.74	0.69	
N (%)below cut-point	494 (50.1)	554 (56.1)		410 (49.3)	518 (62.3)	

Table 1. Comparing the performance of alm/weight% and ALM/BMI in predicting primary endpoints (CVD, fragility fracture, or all cause mortality) using ROC curve. ALM, appendicular lean mass; BMI, body mass index; AUC, the area under the curve; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio. *statistical significance ($p < 0.001$).

males and females. Notably, these indices consistently performed well across both genders, supporting their broad applicability.

Models are adjusted for age, smoking status, alcohol consumption, and the severity of diabetes-related complications (i.e., diabetes duration, HbA1c and DCSI score). The CVD model is additionally adjusted for other established CV risk factors (i.e., LDL-C, HBP and prior CVDs), and the fragility fracture model is additionally adjusted for prior fractures and other body composition factors [i.e., T score ≤-2.5 (at the lumbar spine, femur neck, or total hip)].

HR, hazard ratio; CI, confidence interval; ALM, appendicular lean mass; AFM, appendicular fat mass; BMI, body mass index; BSA, body surface area; HbA1c, glycosylated haemoglobin; DSCI, Diabetes Complications Severity Index; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; HBP, high blood pressure.

Finally, further investigations were conducted to examine the relationship between ALM/BMI or ALM/weight and secondary endpoints in males and females (Fig. 2). Additional adjustments were made for other established CV risk factors when analyzing the CVD endpoints while considering previous fractures and relevant body composition factors for the fragility fracture endpoints, in addition to the initial adjustments. In males, lower ALM/BMI and lower ALM/weight were significantly associated with an increased risk of both all-cause mortality and CVD. For ALM/BMI, the HR for all-cause mortality risk was 0.996 (95% CI = 0.993–0.999; P = 0.011), and that for CVD risk was 0.998 (95% CI = 0.996–0.999; P = 0.011). Similarly, for ALM/weight, the HR for all-cause mortality risk was 0.865 (95% CI = 0.762–0.983; P = 0.026), and that for CVD risk was 0.909 (95% CI = 0.841–0.983; P = 0.017). On the other hand, in females, lower ALM/BMI was associated with an increased risk of CVD, with an HR of 0.997 (95% CI = 0.994-1.000; P = 0.026), while a lower ALM/weight was found to increase the risk of fragility fracture, with an HR of 0.898 (95% CI = 0.806–0.999; P = 0.048).

Predictive performance between ALM/BMI and ALM/weight

ROC curve analysis was employed to assess the predictive performance (CVD, fragility fracture, or all cause mortality) of ALM/BMI and ALM/weight for determining patient prognosis (Table 1 and Fig. S5). The results revealed that the optimal cutoff values of ALM/BMI for the primary endpoints were 820.34 g/BMI (0.605 [95% CI, 0.574–0.636]; sensitivity, 69.23%; specificity, 47.37%) for males and 594.71 g/BMI (0.574 [95% CI, 0.539–0.608]; sensitivity, 71.93%; specificity, 41.13%) for females. On the other hand, the optimal cutoff values of ALM/weight for the primary endpoints were 29.18% (0.585 [95% CI, 0.554–0.616]; sensitivity, 61.54%; specificity, 53.02%) for males and 24.02% (0.571 [95% CI, 0.536–0.605]; sensitivity, 60.09%; specificity, 54.56%) for females. Notably, the AUC was slightly greater for both males and females when using ALM/BMI than when using ALM/weight, but the difference was not statistically significant (all $P > 0.05$).

Population phenotypic characteristics across the ALM/BMI tertiles and the ALM/weight%

Tables S3 and S4 show the characteristics of individuals grouped by sex based on ALM/BMI tertiles. Tables S5 and S6 show the characteristics of individuals grouped by sex based on ALM/weight% tertiles.

Within the ALM/BMI tertiles, across both sexes, distinct differences were noted between individuals in the lowest tertile (T1) and those in the highest tertile (T3). T1 individuals tended to be older, with a longer history of diabetes. They also exhibited higher values in terms of BMI, systolic blood pressure, blood uric acid, uACR, and hsCRP levels. Moreover, these patients were more prone to having diabetic nephropathy, had higher DCSI scores, and were more likely to be using renin - angiotensin - aldosterone system inhibitors. In contrast, T1 individuals had lower eGFRs and serum albumin levels.When it came to body composition, compared with T3 individuals, T1 individuals had greater AFM, body fat percentage, VFM, android fat mass, and android/gynoid fat mass ratio, while their ALM and appendicular MFR were lower. Additionally, sex - specific disparities were evident within

the ALM/BMI tertiles. Among males, T1 individuals had a higher probability of having experienced strokes, prior fractures, and periphral artery diseases. They were also more likely to be on antiplatelet therapy, yet had lower hemoglobin levels and femoral neck bone mass. Among females, T1 individuals had a higher incidence of carotid atherosclerosis and lower total hip bone mass than T3 individuals.

In the ALM/weight% tertiles, the clinical characteristics were similar to those observed in the ALM/BMI grouping. However, surprisingly, regarding the incidence of osteoporosis, especially lumbar osteoporosis, individuals in the lower ALM/weight% group were less likely to develop osteoporosis compared to those in the higher ALM/weight% group, and this trend was consistent across both sexes.

Discussion

T2DM is a leading cause of death and disability globally[22], with its impact exacerbated by associated comorbidities such as ASCVD and fragility fractures. Despite the growing recognition of sarcopenia as a critical factor in T2DM-related outcomes, the optimal method for assessing skeletal muscle mass in this population remains unclear. Our study systematically evaluated the impact of six different relative ALM adjustment methods—ALM/height^2, ALM/BMI, ALM/weight, ALM/ BSA, ALM/total body fat mass, and ALM/AFM—on adverse health outcomes in middle-aged and elderly T2DM patients. The results demonstrate for the first time that both ALM/BMI and ALM/weight significantly predict subsequent overall negative outcomes in both males and females, even after adjusting for multiple confounders.

In our study, we compared six methods of ALM to determine the most potent predictor of adverse outcomes in patients with T2DM. Both ALM/BMI and ALM/weight ratios demonstrated clinical utility in identifying the composite endpoint—encompassing all-cause mortality, ASCVD, and fragility fractures—across genders, with AUC values ranging from 0.571 to 0.605. Subgroup analyses using Cox proportional hazards models revealed sex-specific associations: in males, both ratios showed significant correlations with all-cause mortality and ASCVD, whereas in females, ALM/BMI remained associated with ASCVD and ALM/weight ratios specifically correlated with fragility fractures. A related study supports these findings[23]: it showed that obesity with low muscle mass identified by ALM/weight×100 and ASM/BMI had higher adiposity and lower handgrip strength. ALM/BMI was linked to poor physical performance, and ALM/weight×100 to lower bone mineral density(BMD), validating our use of these ratios as predictors. This observation serves as a crucial reminder of the importance of considering sex-specific variations in muscle mass and fracture risk. It is also worth highlighting that in female, ALM relative to total body fat mass and AFM also emerged as the most robust predictors of primary endpoints. These findings indicate that fat-adjusted ALM indices may hold particular importance for females, which is consistent with previous studies[24,25] This phenomenon can potentially be ascribed to differences in fat distribution and the hormonal impact on muscle and bone metabolism. Meanwhile, in male, ALM/BSA also showed superior performance. Although conducted in trans-catheter aortic valve replacement patients, a study[26] found a lower BSA-adjusted psoas muscle mass index was independently associated with 4-year mortality. This implies BSA-adjusted indices may be useful prognostic tools, consistent with our findings on ALM/BSA in males. Despite this, ALM/BMI and ALM/weight were chosen as the primary areas of focus. This selection was grounded in their wide-ranging applicability, simplicity of measurement, and consistent performance across multiple endpoints.

Both a lower ALM/BMI and ALM/weight are significantly associated with poorer metabolic status, more total and regional fat accumulation, and more comorbidities, highlighting their utility as markers for sarcopenia and metabolic dysfunction in T2DM patients. For instance, T1 individuals are older, have elevated levels of hsCRP, blood uric acid, and uACR, higher DCSI scores, and lower albumin levels. These findings are consistent with research demonstrating that low muscle mass is associated with chronic inflammation, poor nutrition, and diabetes complications, all of which are in line with the pathophysiological mechanisms of sarcopenia presented in studies[27]. Consequently, these individuals face a higher risk of adverse health outcomes. Moreover, their higher BMI, greater fat mass, and lower MFR fit the concept of SO, which exacerbates metabolic dysfunction and heightens health risks in T2DM patients[28,29].Previous studies have also revealed that changes in skeletal muscle mass, as defined by ALM/BMI or ALM/weight, are associated with hepatic steatosis over a six-year period in patients with nonalcoholic fatty liver disease[30]. Building on these findings, it is reasonable to hypothesize that the associations seen in T2DM patients and those with non-alcoholic fatty liver disease share underlying biological mechanisms. Mechanistically, this association can be explained by several factors. First, individuals with lower ALM/BMI and ALM/weight have higher visceral fat mass, which is linked to insulin resistance, inflammation, and increased cardiovascular risk. Second, excess fat mass may lead to muscle fat infiltration, associated with reduced muscle strength, higher fracture risk, and increased mortality[31–33]. Third, aging and metabolic dysregulation in T2DM may promote abnormal differentiation of mesenchymal stem cells (MSCs), causing imbalances in muscle, fat, and bone tissue homeostasis[34–36]. These mechanisms together contribute to the observed association between low ALM/BMI and ALM/weight and adverse outcomes.

Our study reveals important sex-specific differences in the predictive ability of ALM/BMI and ALM/weight for adverse health outcomes in patients with T2DM. In males, both ALM/BMI and ALM/weight are strong predictors of all-cause mortality and ASCVD. This suggests that muscle mass relative to body size or weight plays a critical role in determining cardiovascular and overall health outcomes in males. In females, ALM/BMI can predict ASCVD but is not significantly associated with all-cause mortality or fragility fractures. In contrast, ALM/weight is a strong predictor of fragility fractures in females but does not predict ASCVD or all-cause mortality. In addition, a study[37] has shown that in male patients with metabolic associated fatty liver disease, lower ALM/weight and ALM/BMI are significantly associated with moderate-to-severe steatosis. Another study[38] found that compared with simple obesity, individuals with low lean mass and obesity, as defined by ALM/weight and ALM/BMI, seem to be at a higher risk of metabolic syndrome. These results strongly support the clinical significance of these two indices in assessing and forecasting the outcomes of metabolic diseases.

The sex-specific predictive abilities of these indices may stem from differences in body composition, hormonal influences, fracture pathophysiology, biological muscle- strength decline, and lifestyle factors between males and females[39,40].

An unexpected finding in our study was that individuals in the lowest tertile of ALM/weight had a lower incidence of osteoporosis, especially lumbar osteoporosis, compared to those in the highest tertile. This pattern held true for both genders, challenging the common assumption that lower muscle mass is linked to a higher risk of fractures. In essence, this apparent contradiction highlights the intricate relationship among muscle mass, fat mass, and bone health. A higher body weight, largely attributable to fat mass, can promote bone formation through mechanical loading, thus boosting BMD. This effect is most noticeable in weight-bearing regions like the lumbar spine. As a result, those in the lowest ALM/weight group might have a higher BMD despite having less muscle mass, likely because of their higher body weight. The existing literature backs up this phenomenon. For example, research by Rinonapoli et al.[41] has demonstrated a positive correlation between higher body weight and BMD. Although muscle mass is a key factor in determining BMD, in the lowest ALM/weight group, the greater fat mass may somewhat counterbalance the negative influence of low muscle mass on BMD. It is this complex interaction that results in a relatively higher BMD in the lowest ALM/weight group. Furthermore, a decrease in muscle mass may elevate the risk of fractures primarily by compromising bone quality (such as bone microarchitecture and strength) rather than BMD in T2DM patients[42]. Consequently, even though individuals in the lowest ALM/weight group have a higher BMD, they still confront a greater risk of fractures due to poor bone quality.

Fragility fractures in T2DM patients have historically received less attention compared to other endpoints such as cardiovascular disease and mortality. This may be due to several reasons. First, the pathophysiology of fractures in T2DM is complex and involves both bone quality and quantity, as well as factors such as neuropathy, hypoglycemia, and falls, which are not always captured in traditional risk assessments[42]. Second, the focus of diabetes management has traditionally been on glycemic control and cardiovascular risk reduction, with less emphasis on bone health[43]. Third, the tools for assessing fracture risk in T2DM patients, such as FRAX, may underestimate risk due to the unique bone metabolism in this population[44]. Given these insights, our study considers the use of composite endpoints, including all-cause mortality, ASCVD, and fragility fractures, to simultaneously emphasize metabolic and functional outcomes. This approach underscores the need for a more comprehensive assessment of health risks in T2DM patients, ensuring that both cardiovascular and musculoskeletal health are prioritized in clinical management.

Our study has several strengths, including a systematic evaluation of six ALM methods, a median follow-up exceeding five years, and the use of DXA for accurate muscle mass measurement. However, some limitations should be acknowledged. First, as a single-center study, our findings may not be fully generalizable to other populations. Second, the lack of data on physical activity limits our ability to account for its influence on muscle mass changes. Third, while we adjusted for multiple confounders, residual confounding may still exist. Finally, the inclusion of multiple ALM indices, while comprehensive, may have introduced complexity; future studies could focus on a narrower set of validated metrics.

Conclusion

Our study offers valuable insights into optimal skeletal muscle mass assessment methods for middle - aged and elderly T2DM patients. We've shown that both ALM/BMI and ALM/weight can predict adverse health outcomes, suggesting their potential as practical, clinically relevant markers for sarcopenia in T2DM. Our findings also emphasize the need for a more comprehensive approach to evaluating health risks in T2DM patients, incorporating both metabolic and musculoskeletal outcomes. Future research should focus on whether early identification and intervention based on ALM/BMI and ALM/weight can improve metabolic flexibility and reduce adverse outcomes in T2DM patients.

Data availability

The data generated and analyzed during this study are available from the corresponding author upon reasonable request.

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B.X.: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing-original draft. B.L.: Data curation, Formal analysis, Investigation, Writing-review & editing. X.C.: Investigation, Methodology, Data curation. F.N.C.: Investigation, Data curation. K.L.: Data curation. MM: Investigation, Methodology. R.L.: Methodology, Software, Validation. B.Z.: Writing-review & editing, Visualization, Funding acquisition, Data curation, Conceptualization.

Declarations

Competing interests
The authors declare no competing interests.

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