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Serum ALT activity and its isoenzymes as potential biomarkers for diagnosis of Sarcopenia in older adults: a retrospective, cross-sectional study

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Abstract

Background Alanine aminotransferase (ALT) is an enzyme crucial for energy and protein metabolism in muscle cells. Despite this, its association with sarcopenia remains inadequately explored. This study aims to investigate the correlation between serum levels of ALT-related indicators (ALT activity, ALT1, ALT2, and ALT1/ALT2 ratio) and sarcopenia measures, as well as to develop a diagnostic model for sarcopenia in older individuals.

Methods This retrospective study assessed 653 older adults (aged ≥ 55 years), 109 of whom were studied for the association of ALT1, ALT2, and ALT1/ALT2 ratio with sarcopenia measures. Muscle mass was measured by dual energy X-ray absorptiometry. Hand grip strength (HGS) was measured with a digital dynamometer, and physical performance was assessed through the 6-meter gait speed and the five-times sit-to-stand test (FTSST). Binary logistic regression analysis was used to evaluate associations between ALT-related indicators (ALT activity and ALT1/ALT2 ratio) and sarcopenia. The diagnostic model was developed using binary logistic regression with backward selection, and the diagnostic performance of the model was evaluated by the receiver operator characteristic curve (ROC) curve.

Results Older adults with sarcopenia exhibited a lower serum ALT activity and a higher ALT1/ALT2 ratio compared to those without sarcopenia. ALT activity tertiles, but not ALT1 or ALT2 tertiles alone, correlated with HGS, gait speed, FTSST, and appendicular skeletal muscle mass index (ASMI), serving as independent protective factors for low HGS, low physical performance, low ASMI, and sarcopenia. Tertiles of the ALT1/ALT2 ratio were significantly associated with HGS and FTSST, and were proved independent risk factors for low physical performance and sarcopenia by binary logistic regression analysis. An optimal Model A (based on ALT activity) was established for sarcopenia to develop a new Logit_P1 ($p < 0.001$). Similarly, an optimal Model B (based on ALT1/ALT2 ratio tertiles) was established for sarcopenia to develop a new Logit_P2 ($p < 0.001$). According to the ROC curve analysis for discriminating sarcopenia,

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the performance of Logit_P2 (area under the curve = 0.830) seemed better than that of Logit_P1 (area under the curve = 0.789), although the difference was not statistically significant ($p = 0.214$).

Conclusions In older adults, a low serum ALT activity level was an independent risk factor for low ASMI, HGS, physical performance, and sarcopenia. The serum ALT1/ALT2 ratio emerged as an independent risk factor for low physical performance and sarcopenia. The new indices, Logit_P1 and Logit_P2, demonstrated diagnostic value for sarcopenia.

Keywords Sarcopenia, ALT, ALT1/ALT2 ratio, Diagnostic performance, Older adults

Background

Sarcopenia is an age-related disease characterized by decreased muscle mass, muscle strength, and physical performance [1]. Studies indicate that the prevalence of sarcopenia ranges from 5.5 to 25.7% [2, 3], and it is anticipated to increase in the future due to population aging [4]. Despite this, there is currently a lack of a simple and quick model or method for evaluating sarcopenia risk in clinical practice [5, 6], which may facilitate the rapid and accurate identification of individuals at risk of sarcopenia among the older population.

Serum alanine aminotransferase (ALT) is a widely used indicator, and its enzyme activity can be easily determined through blood tests in clinical practice [7, 8]. The two main ALT isoenzymes, ALT1 and ALT2, play a role in reversible transamination between alanine and α-ketoglutaric acid, forming pyruvate and glutamate. This process is closely linked to cell energy and protein metabolism [7, 8]. Accumulating evidence from clinical and experimental studies has emphasized the connection between sarcopenia and ALT. Clinical data suggests that total serum ALT activity can serve as an emerging biomarker of frailty in older adults [9–12]. It shows decreased levels in patients with sarcopenia [5, 6] and a positive correlation with handgrip strength [13]. However, the correlation between ALT activity and muscle function remains unclear. Additionally, serum ALT isoenzyme assays have been reported to differentiate between muscle injury and hepatic injury in humans [14, 15], based on the distinct organ-specific expression patterns of ALT1 and ALT2 proteins. This suggests that serum ALT1 and ALT2 may be crucial for sarcopenia screening. Therefore, we hypothesize that ALT and its isoenzymes may be independent protective or risk factors for sarcopenia, and could be developed as potential biomarkers for diagnosis of sarcopenia in older adults.

In this study, we aimed to evaluate the association of ALT activity, ALT1, ALT2, and the ALT1/ALT2 ratio with sarcopenia in older adults. The objective is to provide more comprehensive evidence for assessing the risk of sarcopenia in clinical practice using ALT.

Methods

Study design and participants

This retrospective cross-sectional study assessed patients admitted to the Department of Endocrinology and Metabolism at Shanghai Tenth People's Hospital between November 2020 and June 2023. The recruitment flowchart was presented in Figure S1. Inclusion criteria were age ≥ 55 years, while exclusion criteria comprised: (1) severe organ failure or systemic diseases (such as heart failure, renal failure, respiratory failure, liver failure, hematological disorder, systemic connective tissue disease, and malignant tumors); (2) physical disability or mental illness; (3) diseases known to influence ALT activity in serum, such as hepatitis, fatty liver, malnutrition, cardiomyopathy, cerebrovascular disease, infectious mononucleosis, and pancreatitis; (4) use of hepatotoxic drugs (such as, chlorpromazine, isoniazid, quinine, salicylic acid preparations, and ampicillin); (5) treatment with drugs that may affect muscle (such as glucocorticoids and immunosuppressive drugs); (6) missing data on muscle mass, hand grip strength (HGS), 6-meters gait speed and five times sit-to-stand test (FTSST) leading to a failure to diagnose or exclude sarcopenia; (7) missing data on history of osteoporosis and diabetes; and (8) serum transaminase activity is equal to or more than twice the upper limit of normal (ALT ≥ 80U/L; AST (aspartate aminotransferase) ≥ 70 U/L). Diseases were diagnosed collaboratively by two experienced clinicians. All enrolled populations were defined as the total population, and those in which ALT1 and ALT2 concentrations were measured were defined as the subpopulation. The study received approval from the ethics committee of Shanghai Tenth People's Hospital (22K157), and written informed consent was obtained from all patients requiring such consent.

Measures of Sarcopenia

Sarcopenia was diagnosed in accordance with the 2019 consensus of the Asian Working Group for Sarcopenia [3]. It is defined as low appendicular skeletal muscle mass (ASM), combined with low skeletal muscle strength or physical performance.

Low ASM was identified as an appendicular skeletal muscle mass index (ASMI) less than 5.4 kg/m² in females or 7.0 kg/m² in males. ASMI (kg/m²) was calculated by

normalizing the ASM to height in meters squared. ASM was measured using a dual-energy X-ray absorptiometry Hologic scanner (Hologic Discovery QDR Series; Bedford, MA, USA).

Low skeletal muscle strength was defined as hand grip strength (HGS) < 18 kg in females or 28 kg in males (low HGS). HGS was assessed using a digital dynamometer (CAMRYEH10, Xiangshan, Guangdong).

Low physical performance was defined as a 6-meter gait speed test time of more than 6 s (low gait speed) or an FTSST time of no less than 12 s (low FTSST).

Measurements of biochemical and clinical variables

All blood samples were collected in the early morning after an 8-hour fasting period and subsequently transferred to the clinical laboratory of our hospital. Hepatic function indices, including ALT and AST activity, as well as renal function indices such as creatinine and uric acid levels, were measured. ALT activity was assessed using standard laboratory methods. The test reaction employed for ALT involved the reduction of pyruvate to lactate in the presence of dehydrogenase, accompanied by the oxidation of nicotinamide adenine dinucleotide hydrogen to nicotinamide adenine dinucleotide. The reduction of nicotinamide adenine dinucleotide hydrogen was measured at 340 nm using Roche Cobas C701.

Enzyme-linked immunosorbent assay (ELISA) for serum ALT1 and ALT2 measurements

The blood samples were allowed to clot at room temperature for 30–60 min and were centrifuged for 15 min at 2000 × g. Supernatants were collected and stored at − 80 °C for further testing.

Serum concentrations of ALT1 and ALT2 were measured in 109 participants using human ALT1 and ALT2 ELISA kits from Shanghai Enzyme-Linked Biotechnology Co., Ltd. (Catalog # ml522470V for ALT1 and Catalog # m1522369V for ALT2). The assay range was 5.625 ng/ml to 180 ng/ml. To determine the relative levels of ALT1 and ALT2, the ratio ALT1/ALT2 was calculated.

Statistical methods

Continuous variables were analyzed for normality using Kolmogorov–Smirnov test, and were presented as mean ± standard deviation or median (interquartile ranges). Categorical variables were presented as frequencies and percentages. Two independent samples were compared using either an independent two-sample t-test or the Mann–Whitney U test for continuous variables, and chi-square analyses for categorical variables. The correlation between the two ordinal categorical variables was analyzed using Goodman–Kruskal Gamma analysis. Mantel–Haenszel chi-square analysis was used to analyze the distribution of the tertiles of sarcopenia measures with changes in ALT activity (tertile group) or ALT1/ALT2 ratio (tertile group). Post hoc analysis with a Bonferroni correction were conducted for multiple comparisons. Binary logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for low ASMI, low HGS, low physical performance, and sarcopenia across tertiles of ALT activity in the total population and tertiles of the ALT1/ALT2 ratio in the subpopulations. Analyses were adjusted for confounders in three models: Model 1 (crude); Model 2 (adjusted for age, sex, and BMI); and Model 3 (further adjusted for diabetes and osteoporosis). All statistical analyses were performed using SPSS 20.0 and MedCalc 20.112, and statistical significance was set at $p < 0.05$.

Development of diagnostic models

In the subpopulation, we developed diagnostic models based on ALT activity tertiles and ALT1/ALT2 tertiles, respectively. All covariates in Model 3 were subjected to multivariate binary logistic regression analysis with backward selection to establish the optimal sarcopenia diagnostic model. Consequently, sex and osteoporosis were excluded. The optimal model based on ALT activity tertiles was defined as Logit_P1, and the optimal model based on ALT1/ALT2 tertiles was defined as Logit_P2. The models were formulated as follows:

$$\text{Logit\_P1 (or Logit\_P2)} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n.$$

Here, X_1, X_2, …, X_n represent the respective variables in binary logistic regression model. β_0 represents the intercept, and β_1, β_2, …, β_n represent the coefficients corresponding to the respective variables.

The receiver operating characteristic (ROC) curve was employed to evaluate the discriminative accuracy of the new indices for sarcopenia and to determine the optimal cut-off according to Youden's index. The DeLong test was then utilized to compare the two curves.

Results

Patient characteristics

The study included a total of 653 older adults (Figure S1), comprising 373 without sarcopenia and 280 with sarcopenia. Serum ALT activity was accessible for all participants, with serum levels of ALT1, ALT2, and ALT1/ALT2 ratios available for a subset of 109 individuals (Figure S1) (51 without sarcopenia and 58 with sarcopenia). Table 1 illustrated the baseline characteristics of the study participants. In the overall population, individuals with sarcopenia were significantly older than those without sarcopenia (68.5 (9.0) vs. 65.0 (8.0) years, $p < 0.001$). Older adults with sarcopenia exhibited significantly higher FTSST and significantly lower BMI, ASMI, HGS, and serum levels of ALT and AST compared to their non-sarcopenic counterparts. However, no significant differences were observed in markers of renal function and

Table 1 Clinical characteristics between non-sarcopenia and Sarcopenia in older adults

	Total population (*N* = 653)			Subpopulation (*N* = 109)		
Characteristics	**Non-sarcopenia *N* = 373**	**Sarcopenia *N* = 280**	**p value**	**Non-sarcopenia *N* = 51**	**Sarcopenia *N* = 58**	**p value**
Age, years	65.0 (8.0)	68.5 (9.0)	< 0.001	64.3 ± 5.5	69.8 ± 7.2	< 0.001
Female (n, %)	272, 72.9	202, 72.1	0.825	46, 90.2	51, 87.9	0.706
BMI, kg/m^2	23.8 (4.8)	23.0 (4.4)	0.016	24.7 ± 3.8	23.3 ± 2.8	0.024
Diabetes (n, %)	214, 57.4	171, 61.1	0.342	18, 35.3	28, 48.3	0.171
Osteoporosis (n, %)	193, 51.7	157, 56.1	0.272	40, 78.4	47, 81.0	0.735
ASMI, kg/m^2	5.27 (1.18)	4.80 (0.90)	< 0.001	5.13 ± 0.79	4.60 ± 0.51	< 0.001
HGS, kg	25.4 (10.2)	21.0 (8.1)	< 0.001	23.0 (6.4)	21.0 (8.4)	0.001
Gait Speed, m/s	1.20 (0.23)	0.93 (0.29)	< 0.001	1.17 (0.18)	0.89 (0.24)	< 0.001
FTSST, s	9.53 (2.37)	13.31 (7.14)	< 0.001	9.84 (2.03)	14.26 (15.91)	< 0.001
ALT, U/L	17.9 (11.6)	14.6 (8.3)	< 0.001	17.9 (7.5)	14.5 (9.2)	0.003
ALT1, ng/ml	/	/	/	20.4 (19.3)	24.5 (28.2)	0.229
ALT2, ng/ml	/	/	/	21.8 (23.0)	19.1 (26.0)	0.969
ALT1/ALT2	/	/	/	1.05 (0.37)	1.21 (0.32)	0.001
AST, U/L	17.9 (7.2)	17.4 (5.8)	0.014	18.4 (6.2)	17.3 (5.9)	0.153
Creatinine, umol/L	64.0 (15.0)	64.0 (19.8)	0.428	61.0 (13.0)	62.0 (17.3)	0.590
Uric Acid, umol/L	305 (101)	308 (124)	0.301	307 (51)	300 (128)	0.855

Data are presented as mean ± SD or median (interquartile range) or n (%). Abbreviations: BMI, body mass index; ASMI, appendicular skeletal muscle mass index; HGS, hand grip strength; FTSST, five times sit-to-stand test; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table 2 Correlation analysis of ALT related indicators with measures of Sarcopenia

	ALT activity (*n* = 653)		**ALT1 (*n* = 109)**		**ALT2 (*n* = 109)**		**ALT1/ALT2 (*n* = 109)**	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***
HGS	0.218	< 0.001	-0.072	0.551	-0.090	0.478	-0.253	0.029
Gait Speed	0.218	< 0.001	-0.166	0.226	-0.131	0.335	-0.203	0.110
FTSST	-0.242	< 0.001	0.073	0.557	-0.055	0.662	0.367	0.003
ASMI	0.213	< 0.001	0.001	0.995	0.037	0.774	-0.057	0.655

ALT activity: ALT activity tertiles (Tertile 1 ≤ 13.80 U/L, Tertile 2 13.81–19.80 U/L, Tertile 3 ≥ 19.81 U/L); ALT1: ALT1 tertiles (Tertile 1 ≤ 17.17 ng/ml, Tertile 2 17.18–32.83 ng/ml, Tertile 3 ≥ 32.84 ng/ml); ALT2: ALT2 tertiles (Tertile 1 ≤ 14.79 ng/ml, Tertile 2 14.80-30.23 ng/ml, Tertile 3 ≥ 30.24 ng/ml); ALT1/ALT2: ALT1/ALT2 ratio tertiles (Tertile 1 ≤ 0.99, Tertile 2 1.00-1.22, Tertile 3 ≥ 1.23). Abbreviations: ALT, alanine aminotransferase; HGS, hand grip strength; FTSST, five times sit-to-stand test; ASMI, appendicular skeletal muscle mass index; BMI, body mass index

the prevalence of diabetes and osteoporosis between the two groups. Within the specified subpopulation, neither ALT1 nor ALT2 showed significant differences between the sarcopenia and non-sarcopenia groups. Nevertheless, the ALT1/ALT2 ratio was notably higher in the sarcopenia group.

Correlation analysis of ALT activity, serum levels of ALT1, ALT2, and ALT1/ALT2 ratio with measures of Sarcopenia

Measures of sarcopenia, including ALT activity, ALT1, ALT2, and the ALT1/ALT2 ratio, were analyzed in tertile categories. A significant positive correlation was observed between the tertiles of ALT activity and ASMI, HGS, and gait speed ($r = 0.213$, $p < 0.001$;$r = 0.218$, $p < 0.001$, $r = 0.218$, $p < 0.001$), while a negative correlation was found between ALT activity tertiles and FTSST ($r = -0.242$, $p < 0.001$) (Table 2). The ALT1/ALT2 ratio tertiles were strongly positively associated with FTSST tertiles ($r = 0.367$, $p = 0.003$) and negatively associated with HGS tertiles ($r = -0.253$, $p = 0.029$) (Table 2). Gait speed tertiles were also negatively correlated with ALT1/ALT2, although not significantly ($r = -0.203$, $p = 0.110$). Neither ALT1 nor ALT2 tertiles were significantly associated with sarcopenia measures in the simple correlation analysis.

In the total population (Fig. 1), subjects were divided into three groups based on ALT activity tertiles. Significant differences were found in the proportions of sarcopenia measure grades ($p < 0.001$ for HGS tertiles, $p < 0.001$ for FTSST tertiles, $p < 0.001$ for Gait Speed tertiles, and $p < 0.001$ for ASMI tertiles) among the ALT activity tertile categories. In the subpopulation (Fig. 2), subjects were divided into three groups based on the ALT1/ALT2 ratio tertiles. The frequency of higher HGS tertile grades increased with an elevated ALT1/ALT2 ratio ($p = 0.042$ for HGS), and similar findings were observed for physical performance ($p = 0.004$ for FTSST, $p = 0.112$ for gait speed) but not for gait speed.

A post hoc analysis with a Bonferroni correction was performed to assess whether the differences in sarcopenia measurements were statistically significant. Significant

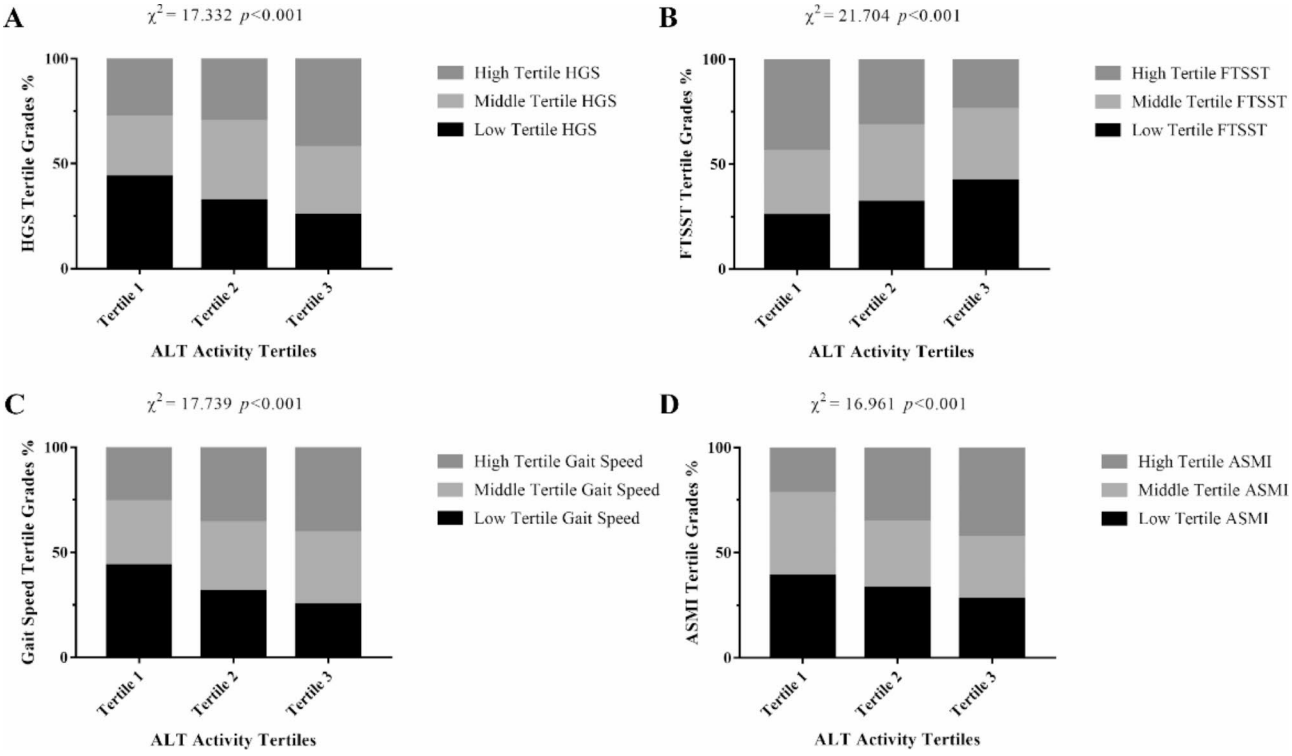

Fig. 1 Distribution of sarcopenia measures tertile grades across ALT activity tertile categories in total population. Evaluation of differences in (**A**) HGS tertile grades, (**B**) FTSST tertile grades, (**C**) Gait Speed tertile grades, and (**D**) ASMI tertile grades among different tertile categories of ALT activity using Mantel-Haenszel Chi-square test. Abbreviations: HGS, hand grip strength; FTSST, five times sit-to-stand test; ASMI, appendicular skeletal muscle index

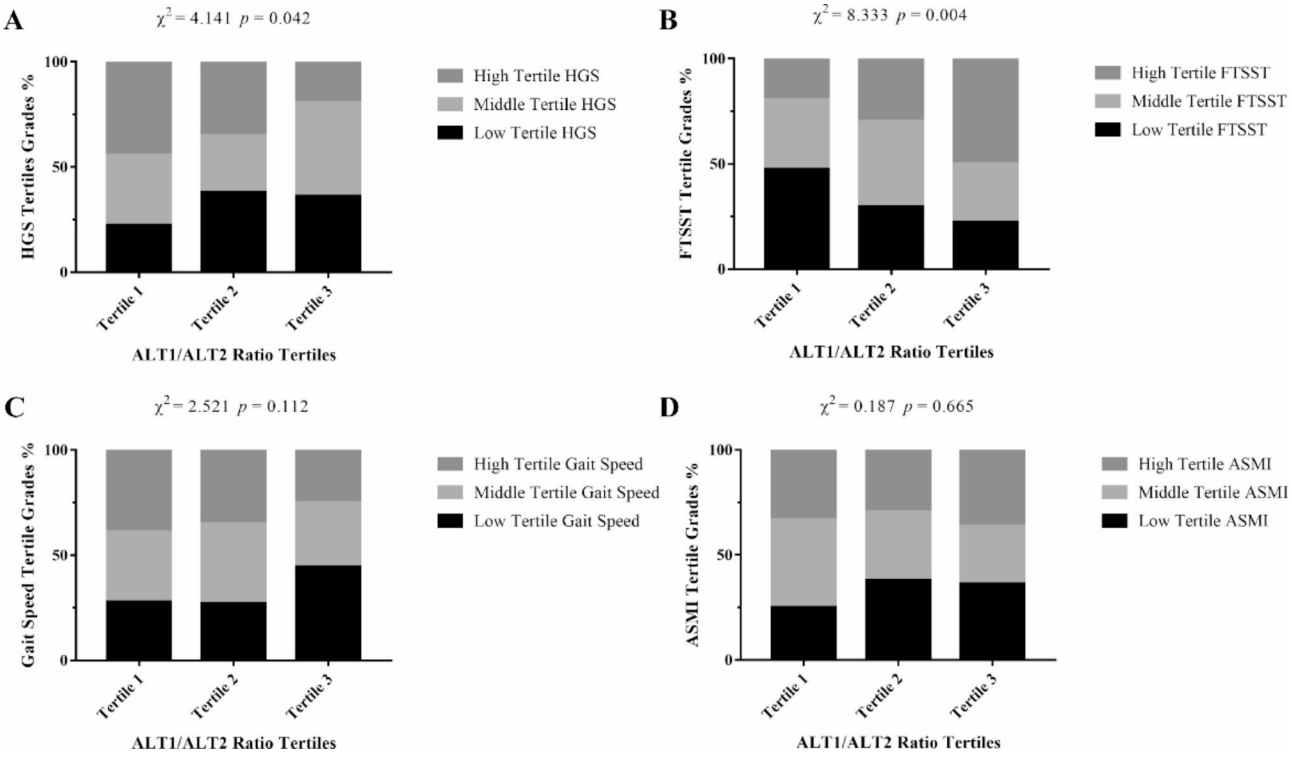

Fig. 2 Distribution of sarcopenia measures tertile grades across ALT1/ALT2 ratio tertile categories in subpopulation. Evaluation of differences in (**A**) HGS tertile grades, (**B**) FTSST tertile grades, (**C**) Gait Speed tertile grades, and (**D**) ASMI tertile grades among different tertile categories of ALT1/ALT2 ratio using Mantel-Haenszel Chi-square test. Abbreviations: HGS, hand grip strength; FTSST, five times sit-to-stand test; ASMI, appendicular skeletal muscle index

differences were observed in the tertiles of HGS, FTSST, Gait Speed, and ASMI when comparing participants with the higher and the lower ALT activity tertiles. Additionally, the difference in FTSST tertiles was also statistically significant between the higher and the lower ALT1/ALT2 tertiles (Table S1).

ALT activity is a protective factor for low HGS, physical performance, ASMI, and Sarcopenia, and ALT1/ALT2 ratio is a risk factor for low physical performance and sarcopenia

Binary logistic regression analysis was performed to assess the association between serum ALT activity (categorized into tertiles) and the ALT1/ALT2 ratio (categorized into tertiles) with the risk of low hand grip strength, impaired physical performance, low ASMI, and sarcopenia (Table 3). After adjusting for age, sex, BMI, diabetes, and osteoporosis (Table 3, Model 3), serum ALT activity emerged as an independent protective factor against low HGS (OR 0.713, 95% CI 0.558–0.912, $p = 0.007$), diminished physical performance (OR 0.653, 95% CI 0.532–0.802, $p < 0.001$), low ASMI (OR 0.559, 95% CI 0.403–0.774, $p < 0.001$), and sarcopenia (OR 0.624, 95% CI 0.508–0.767, $p < 0.001$). In contrast, serum levels of the ALT1/ALT2 ratio were identified as independent risk factors for diminished physical performance (OR 3.417, 95% CI 1.814–6.436, $p < 0.001$) and sarcopenia (OR 2.554, 95% CI 1.399–4.663, $p = 0.002$). Binary logistic regression analysis results, with ALT activity tertiles and ALT1/ALT2 tertiles as categorical variables and the lower tertile as the reference, are provided in Table S2 and Table S3.

Diagnostic value of ALT activity vs. ALT1/ALT2 ratio in serum, combined with other covariables for Sarcopenia in subpopulation

In Model 3, assessing the relationship between ALT activity tertiles and sarcopenia, all covariables underwent multivariate binary logistic regression analysis with backward selection to create an optimal sarcopenia diagnostic model. Consequently, sex and the presence of osteoporosis were excluded (Table S4). The resulting optimal Model A (Nagelkerke $R^2 = 0.361$) for sarcopenia, which included age, BMI, diabetes, and ALT activity tertiles, can be expressed by the equation: Logit_P1 = − 3.675 + 0.167 × age (years) − 0.279 × BMI (kg/m^2) + 0.888 × diabetes (yes = 1, no = 0) − 0.529 × ALT activity tertiles, with ALT activity tertiles referred to as 1 in the low tertile, 2 in the middle tertile, and 3 in the high tertile. Similarly, an optimal model (Model B) based on the ALT1/ALT2 ratio tertiles was established for sarcopenia (Nagelkerke $R^2 = 0.422$), excluding sex and osteoporosis, to develop a new Logit_P2 (Table S5). This index was calculated using the following equation: − 8.582 + 0.185 × age (years) − 0.245 × BMI (kg/m^2) + 0.861 × diabetes (yes = 1, no = 0) + 0.920 × ALT1/ALT2 ratio tertiles, with ALT1/ALT2 ratio tertiles referred to as 1 in the low tertile, 2 in the middle tertile, and 3 in the high tertile. According to the ROC curve analysis for discriminating sarcopenia (Fig. 3), the performance of Logit_P2 was superior to that of Logit_P1 (AUC_{Logit_P1} vs. AUC_{Logit_P2}, 0.789 vs. 0.830, $p = 0.214$), although the difference was not statistically significant. The Youden index indicated that the optimal cutoff value for Logit_P1 was − 0.036, with a sensitivity of 79.3% and a specificity of 66.7% for identifying sarcopenia. The optimal cutoff value for Logit_P2 was − 0.066, with a sensitivity of 86.2% and a specificity of 70.6%.

Discussion

In this study, we discovered that low serum ALT activity independently posed a risk for low ASMI, HGS, physical performance, and sarcopenia. No significant association was observed between individual serum ALT1 or ALT2 levels and measures of sarcopenia. However, the serum ALT1/ALT2 ratio emerged as an independent risk factor for low physical performance and sarcopenia. We subsequently established optimal diagnostic models for sarcopenia based on ALT activity and ALT1/ALT2, resulting in corresponding AUCs of 0.789 and 0.830, respectively.

Protein and energy metabolism disorders play crucial roles in sarcopenia development [16]. Abnormal protein metabolism and inadequate energy supply can contribute to muscle atrophy and decreased muscle contraction [17–19]. Multiple lines of evidence suggest that ALT influences protein and energy metabolism. ALT, an enzyme catalyzing the reversible transfer between

Table 3 Odds ratio of low HGS, low physical performance, low ASMI and Sarcopenia by trisection of ALT activity and ALT1/ALT2

		Low HGS		Low Physical Performance		Low ASMI		Sarcopenia	
		OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
ALT tertiles	Model 1	0.679 (0.535, 0.861)	0.001	0.654 (0.538, 0.794)	< 0.001	0.584 (0.447, 0.763)	< 0.001	0.591 (0.486, 0.720)	< 0.001
	Model 2	0.711 (0.556, 0.909)	0.007	0.654 (0.533, 0.803)	< 0.001	0.574 (0.417, 0.792)	0.001	0.625 (0.509, 0.767)	< 0.001
	Model 3	0.713 (0.558, 0.912)	0.007	0.653 (0.532, 0.802)	< 0.001	0.559 (0.403, 0.774)	< 0.001	0.624 (0.508, 0.767)	< 0.001
ALT1/ALT2 tertiles	Model 1	1.341 (0.785, 2.292)	0.283	2.305 (1.388, 3.826)	0.001	1.266 (0.643, 2.492)	0.495	2.138 (1.301, 3.514)	0.003
	Model 2	1.474 (0.794, 2.738)	0.219	3.135 (1.701, 5.776)	< 0.001	0.969 (0.405, 2.319)	0.943	2.373 (1.323, 4.258)	0.004
	Model 3	1.611 (0.838, 3.097)	0.153	3.417 (1.814, 6.436)	< 0.001	0.973 (0.394, 2.406)	0.973	2.554 (1.399, 4.663)	0.002

Model 1: crude. Model 2: adjusted for age, sex, and BMI. Model 3: adjusted for Model 2 + diabetes, osteoporosis. ALT tertiles: ALT activity tertiles (Tertile 1 ≤ 13.80 U/L, Tertile 2 13.81–19.80 U/L, Tertile 3 ≥ 19.81 U/L); ALT1/ALT2: ALT1/ALT2 ratio tertiles (Tertile 1 ≤ 0.99, Tertile 2 1.00-1.22, Tertile 3 ≥ 1.23). Abbreviations: OR, odds ratio; 95% CI, 95% confidential interval; ALT, alanine aminotransferase; HGS, hand grip strength; ASMI, appendicular skeletal muscle mass index; BMI, body mass index

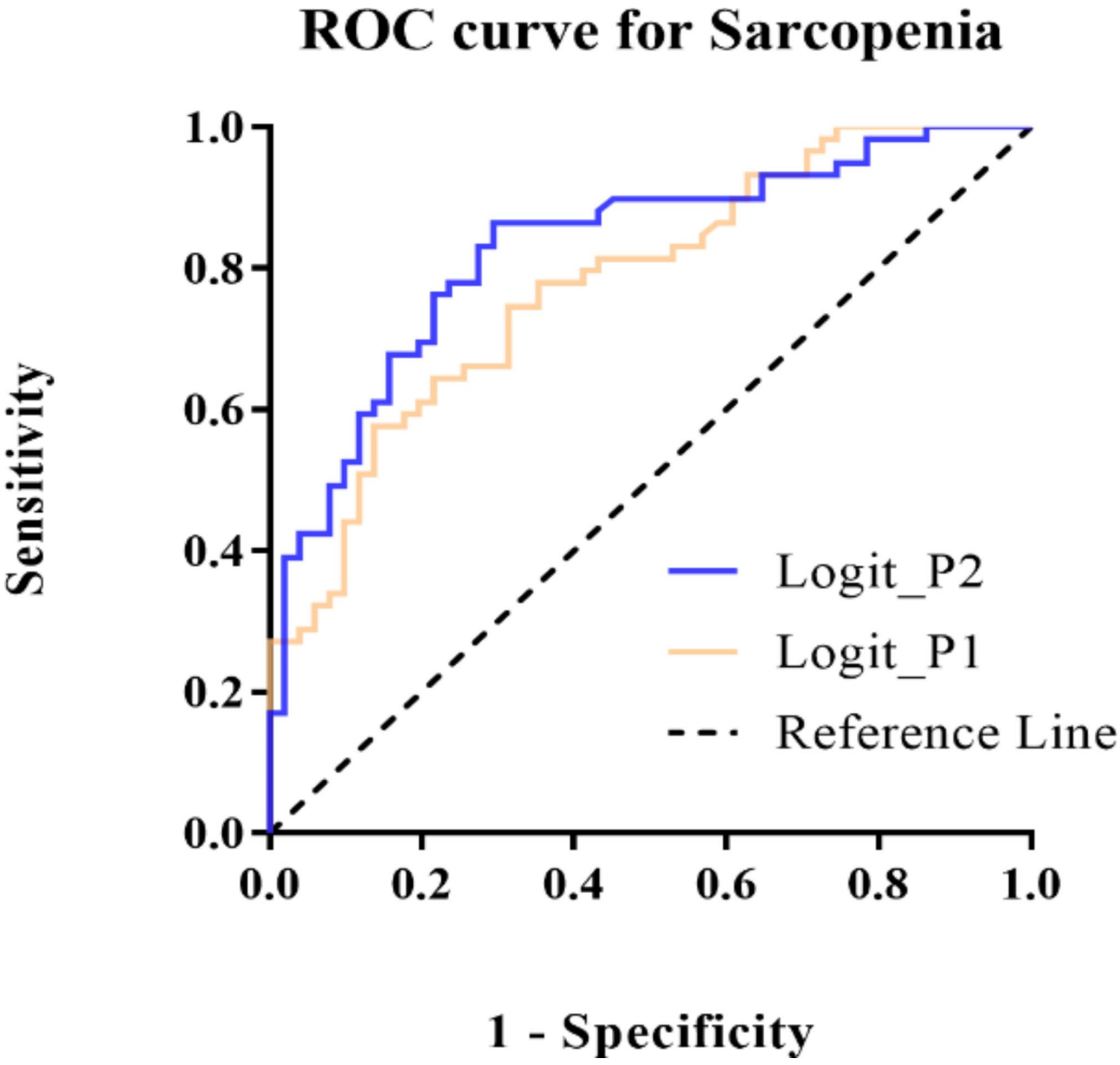

Fig. 3 ROC curve for Logit_P1 (orange line), and Logit_P2 (blue line) in diagnosing sarcopenia. Logit_P1 = − 3.675 + 0.167 × age (years) − 0.279 × BMI (kg/m^2) + 0.888 × diabetes (yes = 1, no = 0) − 0.529 × ALT activity tertiles, with ALT activity tertiles referred to as 1 in the low tertile, 2 in the middle tertile, and 3 in the high tertile, and Logit_P2 = − 8.582 + 0.185 × age (years) − 0.245 × BMI (kg/m^2) + 0.861 × diabetes (yes = 1, no = 0) + 0.920 × ALT1/ALT2 ratio tertiles, with ALT1/ALT2 ratio tertiles referred to as 1 in the low tertile, 2 in the middle tertile, and 3 in the high tertile. Abbreviations: ROC, receiver operating characteristic; ALT, alanine aminotransferase; BMI, body mass index

alanine and α-ketoglutaric acid to form pyruvate and glutamate [7, 20], could provide raw materials for the tricarboxylic acid cycle, thereby enhancing muscle energy supply [21]. Additionally, ALT can be released from the liver and muscles into the bloodstream. Hence, we propose that serum ALT levels may serve as a biochemical marker to estimate the risk of sarcopenia in individuals with normal liver function. This hypothesis is supported by our clinical data, indicating that older adults with sarcopenia exhibited significantly lower serum ALT activity. Furthermore, ALT activity tertiles were positively associated with ASMI, HGS, and gait speed, and negatively associated with FTSST (Tables 1 and 2). Furthermore, we measured and analyzed the association of serum ALT1 and ALT2 concentrations with measures of sarcopenia and found no correlation with HGS, physical performance, or ASMI for ALT1 and ALT2 (Table 2). However, upon analyzing the ALT1/ALT2 ratio, we identified it as an independent risk factor for low physical performance and sarcopenia. In general, ALT1 accounts for more than

90% of the total ALT activity in the serum, whereas ALT2 accounts for less than 10%. Nevertheless, the enzymatic activities of ALT1 and ALT2 exhibit different Km and kcat values [14]. This implies that serum ALT1 or ALT2 alone cannot demonstrate association with sarcopenia, despite ALT activity being relevant. Previous studies have suggested an association between ALT1 and ALT2 with sarcopenia. A recent study discovered that grip strength and the size of the gastrocnemius complex skeletal muscle were higher in BKS-db/db mice with complete liver ALT silencing [22]. Given that ALT1 constitutes the majority of ALT in the liver [7, 22–24], high ALT1 levels could potentially lead to muscle atrophy. Additionally, ALT2 is highly expressed in muscles, and autosomal recessive mutations can induce progressive motor symptoms in humans [7, 23, 24]. A recent Italian study has demonstrated that ALT2 regulates muscle weight and fiber diameter both during rest and under atrophic conditions, acting as a protective factor against muscle atrophy. This indicates that low levels of ALT2 pose a risk for muscle atrophy [25]. These findings suggest a connection between ALT1 and ALT2 and their impact on sarcopenia. Considering the confounding effect between the two factors, where neither factor alone is associated with sarcopenia, it becomes crucial to include both in a multiple regression analysis to determine their collective relationship with sarcopenia.

Recent studies have shown that the ALT1/ALT2 ratio decreases after high-intensity exercise, suggesting a correlation with muscle injury [15]. This ratio is also considered an inflammation-related index for clinical evaluation. In patients with Knodell grades 0 and grade 1, studies have found that the average levels of ALT1 and ALT2 are relatively close. However, as inflammation worsens, ALT2 fluctuates slightly, and ALT1 increases multiple times [26]. Inflammation has been reported to induce muscle atrophy and predispose individuals to sarcopenia [27, 28]. Therefore, it is plausible that the ALT1/ALT2 ratio serves as a risk factor for sarcopenia. We propose that ALT1/ALT2 ratio seems to be associated with physical performance, but not with muscle mass, may stem from divergent biological process. Muscle mass loss is predominantly governed by the imbalance between protein synthesis and degradation, whereas physical performance is a complex trait influenced by a variety of factors, including age-related neurological changes [29]. This distinction may underlie the selective correlation with physical performance. A recent study has found that muscle denervation, a common occurrence in aging, could downregulate ALT2 expression [25], potentially linking the ALT1/ALT2 ratio more closely with physical performance than with muscle mass. While this hypothesis is intriguing, the precise biological mechanisms merit further exploration.

In our pursuit of efficient sarcopenia diagnosis, we explored diagnostic models leveraging ALT activity and the ALT1/ALT2 ratio. This approach aimed to address the challenges associated with time-consuming assessments and low compliance due to the need for extensive muscle measurements, strength tests, and physical performance evaluations [3]. Although the difference in diagnostic performance between Logit_P1 (AUC = 0.789) and Logit_P2 (AUC = 0.830) was not statistically significant ($p = 0.214$), the Youden index of the optimal cut-off value for Logit_P2 surpassed that of Logit_P1. Previous studies exploring hematological indicators, including ALT, for sarcopenia diagnosis presented various laboratory values. The West China Health and Aging Trend Study, for instance, incorporated multiple indicators [26] including fasting insulin, AST/ALT ratio, prealbumin, high-density lipoprotein, free thyroxine 4, adrenal cortisol, and 25(OH)VD, achieving an AUC of 0.742. Other research indicated AUC values of 0.70 for fibrin degradation products [30] and 0.726 for the neurofilament light chain [31]. Given its availability and diagnostic performance, our study suggests a convenient and practical method for sarcopenia diagnosis in older adults during clinical practice.

This study had several limitations. Firstly, while the study was cross-sectional and conducted at a single center, further longitudinal and multicenter studies are necessary to validate our finding and extend our generalizability. Secondly, our study has taken into consideration age, sex, BMI, diabetes and osteoporosis due to the availability of data. However, we recognize that the exclusion of other potential comorbidities, such as frailty, inflammation, nutrition status, and dietary habits, might introduce bias into our comparisons between individuals with and without sarcopenia. Future research should aim to include these variables to provide a more nuanced and holistic understanding of the relationship between ALT levels and sarcopenia. Thirdly, some recent researches suggest the importance of regional muscle mass measurements for the evaluation of sarcopenia [32]. However, our study's methods did not allow for such assessments. The relationship between ALT and its isoenzymes with regional muscle mass measures warrants further exploration in future studies. Fourthly, it is worth mentioning that this study lacks validation, and both internal and external validations are imperative to enhance the credibility of our models in diagnosing sarcopenia.

Despite these limitations, the study boasts several strengths. Firstly, we conducted a comprehensive evaluation of the association between ALT activity, ALT1, ALT2, and the ALT1/ALT2 ratio with muscle mass, muscle strength, physical performance, and sarcopenia. This sheds light on the role of ALT in sarcopenia, providing crucial clinical evidence for further research into

its underlying mechanisms. Secondly, our assessment of physical performance included both gait speed and the FTSST, enhancing the accuracy of sarcopenia diagnosis. This is particularly noteworthy as many studies only consider one of these metrics. Thirdly, we introduce novel approaches for diagnosing sarcopenia in older adults, providing impetus for screening and intervention in community health service organizations.

Conclusion

In older adults aged ≥ 55 years, low serum ALT activity emerged as an independent risk factor for diminished muscle mass, reduced muscle strength, lower physical performance, and sarcopenia. No correlation was identified between individual serum ALT1 or ALT2 levels and sarcopenic measures. Instead, the serum ALT1/ALT2 ratio emerged as an independent risk factor for diminished physical performance and sarcopenia. The newly introduced indices, Logit_P1 and Logit_P2, demonstrated diagnostic value for sarcopenia.

List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASM	appendicular skeletal muscle mass
ASMI	appendicular skeletal muscle mass index
AUC	area under the curve
BMI	body mass index
ELISA	Enzyme-Linked Immunosorbent Assay
FTSST	five times sit-to-stand test
HGS	hand grip strength
OR	odds ratio
ROC	receiver operating characteristic
95% CI	95% confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

H. S. – Conceptualization, funding acquisition, project administration, resources and supervision. J. Z. and N. L. – Data curation, formal analysis, methodology, validation, visualization, writing – original draft and writing – review & editing. J. G., H. M., S. S. and Y. J. – Investigation. C. Q., R. C. and S. Q. – Methodology and supervision. All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsink and approved by the Shanghai Tenth People's Hostipal Ethics Committee (protocol code 22K157 and date of approval: 14 July 2022). Written informed consent was provided by all patients who required informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Footnotes

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