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Original article

Associations between low muscle mass and clinical characteristics of health population in China

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ABSTRACT

Objectives: The primary aim of this study is to discern the association between specific clinical parameters and low muscle mass (LMM). We endeavor to elucidate the determinants of LMM and the predictive potency of individual factors.

Methods: In this retrospective cross-sectional study, we encompassed 450 older adult Chinese participants (252 males and 198 females). Muscle mass quantifications were performed using bioelectrical impedance analysis. Comprehensive data encompassing demographic details (age, sex, height, and weight) and laboratory results (complete blood count, thyroid function, liver function, and renal function) were systematically recorded. Logistic regression models, coupled with receiver operating characteristic curve analytics, were employed to ascertain the variables influencing LMM and to evaluate the predictive validity of each parameter on LMM.

Results: Upon confounding adjustment for age, gender, body mass index (BMI), and free thyroxine (FT4) persisted as a determinant of LMM. Specifically, individuals with an FT4 exceeding 1.105 ng/dL exhibited a 1.803-fold increased propensity for LMM relative to those with FT4 values below the specified threshold. Incorporating age, gender, BMI, and FT4 in the diagnostic algorithm enhanced the precision of LMM. The results differ between men and women. In the male population, we can still observe that FT4 has a certain value in the diagnosis of LMM, but this phenomenon is not found in the female population.

Conclusions: Elevated FT4 concentrations, albeit within clinically accepted limits, are inversely associated with muscle mass. As such, FT4 could be postulated as a potential biomarker for LMM in geriatric individuals, especially in the male group.

1. Introduction

Sarcopenia is a pathological condition chiefly characterized by an age-related decline in skeletal muscle mass, strength, and physiological function. It is a globally prevalent disorder, with the World Health Organization conservatively projecting the number of cases to escalate from over 50 million in 2010 to approximately 500 million by 2050 [1]. Epidemiological investigations, employing the AWGS 2014 criteria in Asian demographics, indicate a variable prevalence ranging from 5.5% to 25.7%, with a pronounced incidence in males [2].

Sarcopenia results in reduced physical activity, which may lead to adverse consequences, such as falls, disability, decreased quality of life, and death [3]. Evidence-based medical data also shows that sarcopenia is an important risk factor for depression [4,5] and other diseases in the older adult population, as it increases the readmission rate, hospital stay time, and the burden on individuals and society [3]. The comprehensive diagnostic process for sarcopenia necessitates the assessment of muscle mass, strength, and physical function, making conventional methods somewhat intricate and time-inefficient. Therefore, there exists a pressing need for more practical and swift diagnostic measures, especially considering that Low Muscle Mass (LMM) is a pivotal diagnostic criterion for sarcopenia, and its early identification and management can decelerate the progression of the condition [6].

Several imaging modalities, including magnetic resonance imaging

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(MRI), computed tomography (CT), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA), are extensively utilized for measuring appendicular skeletal muscle mass. MRI and CT scans, being the gold standards for non-invasive muscle mass evaluations, offer precise differentiation between muscle and adipose tissues. However, their high operational costs and intricate equipment requisites limit their clinical application. Conversely, DXA and BIA are more clinically favored due to their convenience and non-radiative nature, with BIA being particularly noted for its accessibility.

Additionally, the etiopathogenesis of sarcopenia is multifaceted, encompassing not just the loss of muscle mass but also perturbations in endocrine and metabolic functions [7,8]. Numerous blood biomarkers have been identified to have contributory roles in sarcopenia's development [9]. Thus, this study primarily concentrates on elucidating the relationships between blood biochemical markers and LMM in an endeavor to identify pertinent markers conducive to the diagnostic process of LMM.

2. Methods

2.1. Study design and participants

We conducted a retrospective cross-sectional study involving participants who voluntarily attended the annual health screening program at Huzhou Central Hospital, Zhejiang, China, between October 2021 and February 2023. The study design and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethics Committee of Huzhou Central Hospital—202209030-01) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent for participation was obtained from all subjects.

Inclusion Criteria: (1) Individuals aged $\geq$ 60 years. (2) Those who underwent blood routine tests, thyroid function tests, liver function tests, kidney function tests, and body composition measurements utilizing InBody 570 (InBody Co., Ltd. Seoul, South Korea). Exclusion Criteria: (1) Individuals with overtly abnormal thyroid function tests. (2) Individuals with documented history of thyroid-associated conditions including hypothalamic-pituitary diseases, autoimmune disorders, sarcoidosis, and amyloidosis. (3) Individuals on medications impacting thyroid function such as thyroxine replacement therapy, amiodarone, dopamine, glucocorticoids, among others. (4) Individuals diagnosed with infectious diseases, malignancies, or other catabolic conditions. (5) Individuals with significant organ failure including respiratory, cardiac, renal, or hepatic. (6) Individuals with compromised mobility or those who are bedridden.

2.2. Study methods

Participants' demographic data, including age, height, and weight, were collected. The body mass index (BMI) was deduced using the formula: weight (kg) divided by the square of height (m^2). Additionally, we also collected the results of blood routine, liver function, kidney function, and thyroid function. Measurements of blood routine test was performed using Sysmex XN-9000 Hematology Analyzer. Liver function and kidney function were performed using Abbott ARCHITECT C1600 Clinical Chemistry Analyzer. Thyroid Function was performed using Abbott ARCHITECT i2000SR Immunoassay Analyzer. The precision of tests for TT3, TT4, FT3, FT4, and TSH is such that the total coefficient of variation (CV) is less than or equal to 10%. The human body composition measurement by InBody 570 Body Composition Analyzer.

Criteria for LMM: Skeletal muscle mass was gauged using the Inbody 570, employing BIA. As per the standards set by the Asian Working Group on Geriatric Sarcopenia (AWGS, 2019), an Appendicular Skeletal Muscle Mass Index (ASMI) of < 7 kg/m^2 in males and < 5.7 kg/m^2 in females is classified as LMM [2].

Conversion of Continuous variables: A continuous variable directly in logistic regression allows us to understand how the risk of the outcome event changes with each unit increase of the variable. However, such an interpretation can often be clinically abstract. Therefore, we will convert the continuous variables that are shown to be significant in binary logistic regression analysis into dichotomous variables, which offers a more clinically relevant assessment of risk. To determine the most diagnostically efficient cut-off value, we conducted a receiver operating characteristic (ROC) curve analysis with the continuous variables and identified the optimal threshold. We then used this cut-off value to categorize continuous variables into 2 distinct groups.

Combination index setting: We utilized the predictive probabilities derived from the binary logistic regression to construct the ROC curve for the Combination index. These probabilities were computed using the established formula from the binary logistic regression analysis.

Logit (P) = constant + regression coefficient 1 * variable 1 + regression coefficient 2 * variable 2 + …

$$\text{Prediction prabability} = \frac{e^{Logit(P)}}{1 + e^{Logit(P)}}$$

2.3. Statistical analysis

Data were represented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for skewed continuous variables, and both absolute and relative frequencies for categorical variables. The association between LMM and potential determinants was scrutinized using binary logistic regression, incorporating variables with P-values < 0.05 in univariate analyses. The predictive efficacy of each factor for LMM was assessed using the Receiver Operating Characteristic (ROC) curve. All analyses were executed using SPSS version 21.0, with a significance threshold set at $\alpha = 0.05$.

3. Results

3.1. Clinical characteristics comparison: LMM group vs. non-LMM group

The prevalence of LMM was observed to be 23.41% (59/252) in male participants and 14.14% (28/198) in female participants. Notable disparities were found between the LMM and non-LMM cohorts concerning age, sex, BMI, free triiodothyronine (FT3), free thyroxine (FT4), and the FT3/FT4 ratio. Conversely, parameters such as hemoglobin, white blood cell count, creatinine, uric acid, total triiodothyronine (TT3), total thyroxine (TT4), and thyroid-stimulating hormone (TSH) exhibited no significant distinctions between the 2 groups. Detailed data can be referenced in Table 1.

3.2. Logistic regression analysis associated with LMM

Using LMM as the dependent variable, binary logistic regression was conducted, factoring in independent variables like age, sex, BMI, FT3, FT4, and the FT3/FT4 ratio. The findings indicated that increasing age, male gender, and elevated FT4 concentrations posed as risk determinants for LMM, whereas higher BMI served as a protective factor. The logistic model showcased significant statistical relevance with $\chi^2 = 180.74$, $P < 0.001$, and was proficient in classifying 87.3% of participants accurately. When categorizing FT4 as a dichotomous variable and adjusting for age, sex, and BMI, individuals exhibiting FT4 levels exceeding 1.105 ng/dL faced a 1.803-fold augmented risk of LMM relative to those below this threshold. Detailed data can be referenced in Table 2, Table 3.

3.3. Predictive efficacy of variables for LMM

Among the risk variables examined, BMI proffered the highest Area Under the Curve (AUC) for LMM prediction at 0.85. However, it exhibited

Table 1
Comparison of clinical characteristics between LMM group and non-LMM group.

	LMM group	Non-LMM group	T-value/Z-value/χ^2 value	P-value
Age, yrs	68.00 (64.00, 74.00)	65.00 (62.00, 68.00)	−4.90	< 0.001
Gender (male)	59 (67.82%)	193 (53.17%)	6.11	0.013
BMI, kg/m^2	20.50 (19.00, 22.40)	24.50 (22.40, 26.40)	−10.16	< 0.001
Hemoglobin, g/L	138.20 ± 14.37	141.53 ± 13.88	1.96	0.53
White blood cells, ×10^9/L	5.50 (4.50, 6.60)	5.50 (4.80, 6.60)	−1.18	0.24
Creatinine, μmol/L	72.50 (65.40, 83.30)	71.80 (64.70, 80.40)	−0.58	0.56
Uric acid, μmol/L	346.70 (259.30, 393.50)	340.60 (293.30, 398.20)	−1.50	0.13
FT3, pg/mL	2.85 (2.66, 3.06)	2.94 (2.72, 3.14)	−2.05	0.04
TT3, ng/mL	0.96 (0.86, 1.08)	0.98 (0.89, 1.08)	−1.326	0.19
FT4, ng/dL	1.06 (0.96, 1.15)	1.02 (0.95, 1.09)	−2.58	0.01
TT4, μg/dL	7.63 (6.79, 8.74)	7.38 (6.59, 8.31)	−1.74	0.083
TSH, μIU/mL	1.90 (1.34, 2.92)	1.81 (1.22, 2.67)	−0.97	0.33
FT3/FT4 ratio	2.73 (2.41, 2.95)	2.89 (2.60, 3.16)	−3.34	0.001

Numeric variables following the normal distribution are shown as mean ± SD and compared with independent-samples T test. Numeric variables that do not follow the normal distribution are shown as median (25% percentile, 75% percentile) and compared with non-parametric test. Categorical variables are shown as proportion (%) and compared with Chi-squared (χ^2). LMM, low muscle mass; BMI, body mass index.

Table 2
Binary logistic regression analysis of LMM.

Variable	OR value (95%CI)	P-value
Age, yrs	1.152 (1.093–1.215)	< 0.001
Gender (male)	3.254 (1.708–6.199)	< 0.001
BMI, kg/m^2	0.499 (0.425–0.586)	< 0.001
FT3, pg/mL	–	0.260
FT4, ng/dL	23.153 (1.451–369.513)	0.026
FT3/FT4 ratio	–	0.254

LMM, low muscle mass; BMI, body mass index.

Table 3
Logistic regression analysis of LMM (FT4 as dummy variable).

Variable	OR value (95%CI)	P-value
Age, yrs	1.156 (1.096–1.220)	< 0.001
Gender (male)	3.125 (1.637–5.966)	0.001
BMI, kg/m^2	0.498 (0.423–0.586)	< 0.001
FT4 (greater than 1.105 ng/dL)	2.803 (1.434–5.479)	0.003

LMM, low muscle mass; BMI, body mass index. Binary logistic regression results show that FT4 is an independent risk factor for LMM. The risk of LMM changes with each unit increase of FT4. However, such an interpretation can often be clinically abstract. Therefore, we categorized FT4 as a dichotomous variable, which offers a more clinically relevant assessment of risk. To determine the most diagnostically efficient cut-off value, we conducted a receiver operating characteristic (ROC) curve analysis with FT4, which identified 1.105 ng/dL as the optimal threshold. We then used this cut-off value to categorize FT4 levels into 2 distinct groups.

a specificity of a mere 30.9%. The AUC for LMM prediction, when amalgamating age, sex, BMI, and FT4, stood at 0.91. At a combined index cut-off of 0.27, the sensitivity and specificity for predicting LMM were 81.6% and 88.2%, respectively. Detailed data can be referenced in Table 4.

Table 4
Predicting value of each factor for LMM.

	AUC (95%CI)	Cut-off value	Sensitivity	Specificity
Age, yrs	0.67 (0.60–0.73)	66.5	58.6%	66.1%
Gender	0.57 (0.51–0.64)	–	–	–
BMI, kg/m^2	0.85 (0.81–0.90)	22.85	87.4%	30.9%
FT4, ng/dL	0.59 (0.52–0.66)	1.105	40.2%	79.3%
Combination index	0.91 (0.87–0.94)	0.27	81.6%	88.2%

LMM, low muscle mass; BMI, body mass index. Combination index was calculated by logistic regression equation.
We utilized the predictive probabilities derived from the binary logistic regression to construct the ROC curve for the combination index. These probabilities were computed using the established formula from the binary logistic regression analysis.
Logit (P) = 0.610 + 0.142 * age + 1.180 * sex (male = 1, female = 0) - 0.695 * BMI + 3.142 * FT4.
Cut-off value was the point which has good sensitivity and specificity at the same time.

3.4. Difference in male and female

We conducted separate studies on male and female populations. We found that in the male population, FT4 remains an independent risk factor for diagnosing LMM. When FT4 is combined with BMI and age, the AUC for diagnosing LMM can reach 0.92. However, this phenomenon was not observed in the female population. Detailed data can be referenced in Table 5.

4. Discussion

In the present study, we discerned specific clinical characteristics associated with LMM in an older adult Chinese demographic. Our findings indicated that individuals with LMM were notably older and exhibited lower BMI, FT3, and FT3/FT4 values ($P < 0.001$ for age, BMI, and FT3/FT4; $P = 0.040$ for FT3). A significant male predominance and elevated FT4 levels were also observed among participants with LMM ($P = 0.013$ for gender; $P = 0.01$ for FT4). Logistic regression analyses emphasized that FT4 elevation was consistently related to LMM even after controlling for other variables, especially in men. Specifically, those with FT4 levels exceeding 1.105 ng/dL demonstrated a roughly twofold augmented risk for LMM compared to their counterparts with lower FT4 levels. Such findings propose that FT4, being intrinsically linked with LMM, might serve as a potent diagnostic marker for LMM. Additionally, based on univariate and multivariate analyses, our study established ROCs to delineate clinical attributes indicative of LMM. Herein, BMI presented the highest AUC, succeeded by age, FT4, and gender, with a composite AUC of these parameters reaching 0.91, signifying enhanced predictive prowess for LMM. Clinically, when FT4 exceeds 1.105 ng/dL or when the combined index surpasses 0.27, a comprehensive assessment encompassing muscle strength and physical functionality is advocated, potentially optimizing sarcopenia screening.

Sarcopenia, predominantly an age-related ailment, is chiefly characterized by deteriorating muscle mass and function. Its prevalence has been escalating rapidly in contemporary times. Concurrently, thyroid dysregulation, another age-correlated endocrine perturbation, influences skeletal muscle—a primary target of thyroid hormones—thereby modulating muscle genesis, contraction, and metabolism. This has implications in various muscle-associated pathologies [10]. A longitudinal investigation on older adult men (mean age 74.43 ± 6.92 years) with standard thyroid functionality revealed that elevated FT4 levels initially were inversely related to lower limb function 3 years later,

Table 5
Difference in male and female.

Male				Female			
Binary Logistic regression analysis of LMM							
	OR value (95%CI)		P-value		OR value (95%CI)		P-value
BMI, kg/m^2	0.53 (0.43, 0.64)		<0.001	BMI	0.58 (0.44, 0.75)		< 0.001
FT4, ng/dL	34.82 (1.05,1158.80)		0.047	Uric acid	0.99 (0.98, 1.00)		0.02
Age, yrs	1.17 (1.09, 1.25)		<0.001				
ROC of Combination index							
	AUC (95%CI)	Cut-off value	Sensitivity/Specificity		AUC (95%CI)	Cut-off value	Sensitivity/Specificity
Combination index	0.92 (0.87,0.96)	0.33	81%/91%	Combination index	0.86 (0.79,0.94)	0.19	75%/85%

LMM, low muscle mass; BMI, body mass index; AUC, area under the curve. Combination index was calculated by logistic regression equation.
We utilized the predictive probabilities derived from the binary logistic regression to construct the ROC curve for the combination index. And cut-off value was the point which has good sensitivity and specificity at the same time.

albeit no such correlation emerged for TSH and FT3 [11]. Various cross-sectional inquiries have echoed the sentiment that an elevated FT4 constitutes a risk element for sarcopenia [12,13], mirroring our study's outcomes. Our research infers that even within the bounds of typical thyroid functionality, an ascent in FT4 might be inversely proportional to muscle mass, furnishing an invaluable metric for early sarcopenia detection. Furthermore, managing subclinical hyperthyroidism may amplify muscle mass, offering novel therapeutic prospects for sarcopenia. These observations potentially correlate with a senescence-induced diminution in 5′-deiodinase activity, which may either be inherently age-associated or tethered to nonthyroidal maladies. An escalated cytokine profile in aging might also play a pivotal role, given the documented inhibitory effects of cytokines like TNF-α, IL-1, and IL-6 on 5′-deiodinase activity [14].

Existing literature posits that either FT3 [15,16] or the FT3/FT4 ratio [17,18] might offer a more comprehensive understanding of frailty's impacts and muscle functionality in the older adult. Additionally, reduced FT3 levels have been observed in sarcopenia patients. However, our findings highlight that while both FT3 and the FT3/FT4 ratio were indeed lower in the low muscle mass (LMM) cohort compared to the non-LMM group, neither was identified as an independent risk factor for LMM. This is in contrast to our research findings and could be explained by the following reasons. Firstly, animal studies have demonstrated that T3 influences metabolic processes in muscles undergoing starvation. Specifically, T3 has been shown to counteract muscle wasting induced by starvation. Yet, it does not inhibit the activation of primary catabolic pathways, ie, the ubiquitin-proteasome or the autophagy-lysosomal systems, nor does it promote the synthesis of new muscle in muscles that are starved [19]. Secondly, some studies have indicated that subclinical hyperthyroidism-but not subclinical hypothyroidism-impacts muscle mass and strength in the older adult. For example, in an older adult Korean cohort, higher T4 levels have been associated with sarcopenia [20], aligning with our results. This could be due to the more stable nature of FT4. Thirdly, the differences in conclusions may arise from the diverse demographics, including race, gender, age, and baseline health conditions, of the study populations involved.

Several limitations are noteworthy in the present study. Firstly, our study was a retrospective cross-sectional analysis of individuals who voluntarily participated in an annual health screening program. This program typically includes standard tests such as blood routine test, liver function test, kidney function test, and thyroid function tests. Other hormone assays, which may also affect muscle, were not part of the annual health screenings for these participants, so we just focused on these specific variables in this study. Secondly, the research was confined to a singular center with a restricted participant size. Although we identified a difference between the LMM group and the non-LMM group, the disparity was slight and varied between males and females. This may be attributed to the smaller number of female participants compared to males in our study. We expect that a larger sample size would reveal a more significant difference, potentially leading to the same conclusion in both males and females. Thirdly, attributable to the retrospective cross-sectional design, prognostic follow-up of subjects was absent. Consequently, differentiating sarcopenic from non-sarcopenic participants among the LMM cohort proved challenging, primarily due to the absence of comprehensive muscle strength and functional data. As such, while the study investigated associations with LMM, implications on muscle strength or function remain elusive. Lastly, dietary patterns, a potential determinant of skeletal muscle mass, were unexplored. Caloric intake might directly influence the DIO2 pathway and thus exert an indirect effect on thyroid hormones [21].

In light of these, future endeavors necessitate a multicentric approach with augmented sample sizes and a prospective design, which encapsulates data on muscle strength, physical functionality, other hormone and dietary habits.

5. Conclusions

FT4 is an independent predictor for LMM, even after adjusting for the effects of other factors, especially in older adult male. A diagnostic amalgamation of age, gender, BMI, and FT4 could refine LMM identification. Enhanced screening efficacy for sarcopenia might be attainable when FT4 surpasses 1.105 ng/dL or the cumulative index exceeds 0.27.

CRediT author statement

Yunfei Pan: Data Curation, Formal analysis, Writing – Original draft. **Mengjie Hu**: Writing – Review & Editing. **Feimin Zhao**: Writing – Review & Editing, Funding acquisition. **Jingjing Ren:** Writing – Review & Editing, Supervision.

Conflicts of interest

The authors declare no competing interests.

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