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ORIGINAL RESEARCH

Analysis of Risk Factors for the Association of Sarcopenia in Patients with Type 2 Diabetes Mellitus

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Background: Previous studies have shown that the prevalence of sarcopenia in patients with type 2 diabetes mellitus (T2DM) has increased significantly over the years. However, the risk factors for the association of sarcopenia in patients with T2DM are unknown. Therefore, we attempted to investigate the risk factors through measurement and analysis of the patients' data from April 2020 to April 2022.

Methods: A total of 334 hospitalized patients with T2DM were divided into sarcopenia group (n=101) and non-sarcopenia group (n=233). Clinical factors were compared between the two groups and also between the two genders. Receiver operating characteristic curve (ROC) was used to analyze the ROC diagnostic ability of related factors in sarcopenia.

Results: (1) Among the 334 patients, the overall prevalence of sarcopenia was 30.2%; 41.3% in men and 20.1% in women. (2) The multifactorial logistic regression analysis showed that gender (specifically for men; OR=4.997, 95% CI: 2.611–9.564), low body mass index (BMI) (OR=1.525, 95% CI: 1.353–1.718), lower 25(OH)D levels (OR=1.076, 95% CI:1.036–1.117), and lower IGF-1 (OR=1.013, 95% CI:1.006–1.020) were independent risk factors ($P < 0.05$). (3) ROC curve analysis results showed that BMI, 25 (OH) D, IGF-1, and testosterone (for men) had predictive significance for sarcopenia with T2DM ($P < 0.05$). However, the AUC of 25 (OH) D, IGF-1 and testosterone (for men) were all <0.7, while the AUC of BMI and the combined factors were all >0.7, has great predictive significance.

Conclusion: The prevalence of sarcopenia in hospitalized patients with T2DM is higher in men than in women. Low BMI and lower serum levels of 25 (OH) D and IGF-1 are risk factors of sarcopenia in patients with T2DM. Low BMI, 25(OH)D, IGF-1, and testosterone (for men) all contributed to the prediction of sarcopenia, among which BMI and combined factors were more significant.

Keywords: risk factors, sarcopenia, T2DM, body mass index, 25 (OH) D, IGF-1

Introduction

Two common old age-related diseases in the Chinese population are type 2 diabetes mellitus (T2DM) and sarcopenia, which is a degenerative disease characterized by the loss of skeletal muscle function and mass.[1] Skeletal muscle accounts for 40% of the body's total weight and is an important part of the motor system as almost all of the body's activities are controlled by the contraction of the skeletal muscles. In addition, skeletal muscle is one of the major utilizers of glucose in the body and is the largest insulin-sensitive tissue, due to which it plays a very important role in energy and metabolic homeostasis.[2] Therefore, the skeletal muscle plays an important role in T2DM.

People with T2DM are at high risk for developing sarcopenia, and the prevalence of sarcopenia in T2DM patients is much higher than that in the normal population.[3]

Findings from the Asian Working Group for Sarcopenia (AWGS) showed a prevalence of 15% in Chinese (>60 years) and Japanese (≥65 years) adults with T2DM.[4] Diabetes and sarcopenia interact with each other. The disorder of glucose metabolism promotes the catabolism of the body and the breakdown of muscle protein, thus leading to the decline of muscle function and muscle content.[5] The decrease of muscle content will further aggravate insulin resistance, and the insulin resistance of muscle will inhibit the energy metabolism of muscle cell mitochondria and affect the normal contraction function of muscle tissue.[6] At

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the same time, the elderly are prone to unbalanced nutritional intake and insufficient protein intake, and inappropriate diabetes diet control will further increase the risk of malnutrition, resulting in a significant decline in muscle mass and strength. As a chronic metabolic disorder, T2DM greatly impacts the quality of life of a patient; for patients with T2DM who also develop sarcopenia, the risks of developing disabilities, falling and fracturing bones, and even mortality, are greatly increased.[7] The sarcopenia leads to major threats to the health and well-being of patients with T2DM. Therefore, in recent years, some scholars believe that skeletal muscle damage caused by T2DM may be a new complication of diabetes.[8] Although there have been some studies on diabetic sarcopenia, the risk factors are still unclear and further research is needed. Therefore, the present study explored the risk factors for sarcopenia in patients with T2DM by analyzing the prevalence and clinical data of sarcopenia with T2DM in 334 patients. The significance of related factor in predicting sarcopenia was also discussed.

Materials and Methods

Research Subjects

Clinical data for a total of 334 patients aged ≥60 years with T2DM who were consecutively admitted to the Department of Endocrinology, the Second Affiliated Hospital of Anhui Medical University from April 2020 to April 2022. A total of 160 men and 174 women were included. All subjects signed informed consent, and the study was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (YX2022-026) and complied with the Declaration of Helsinki.

Inclusion and Grouping Criteria

1. All subjects had to meet the diagnostic criteria for diabetes mellitus as described by the World Health Organization (WHO) in 1999.[9]
2. According to the AWGS consensus standards (2014), all the patients included in this study were divided into two groups: the sarcopenia group (n = 101; 66 men and 35 women) and the non-sarcopenia group (n = 233; 94 men and 139 women).

Diagnostic Criteria for Sarcopenia as Described by the AWGS (2014)

1) Decreased muscle mass: dual-energy X-ray absorptiometry (DXA) was used to determine skeletal muscle mass, and sarcopenia was suspected if the skeletal muscle mass index (appendicular skeletal mass index (ASMI) = skeletal muscle weight (kg)/height of limbs^2(m)^2)) was <7.0 kg/m^2 for men and <5.4kg/m^2 for women; additionally, sarcopenia was also suspected if the bioelectrical impedance analysis (BIA) to determine ASMI showed values of <7.0kg/m^2 for men and <5.7kg/m^2 for women. 2) Decreased muscle function: sarcopenia was diagnosed if the daily walking speed was <0.8m/s. 3) Decreased muscle strength: sarcopenia was suspected if the grip strength assessed in the dominant hand was <26 kg for men and <18 kg for women. If a patient was suspected to have sarcopenia in criteria 1) and 2) or 1) and 3) or all three, the patient was diagnosed as having sarcopenia.[10]

Diagnosis of sarcopenia: if reduced grip strength (<26 kg for men and <18 kg for women) and walking speed (<0.8m/s) were used as screening index, a DXA body tissue composition test was performed; if the test results were <7.0 kg/m^2 for men or <5.4 kg/m^2, sarcopenia was diagnosed.

Exclusion Criteria

1. Patients with Type 1 diabetes mellitus;
2. Patients with severe acute and chronic complications caused by diabetes, such as diabetic ketoacidosis, hyperglycemic hyperosmolar status, diabetic foot;
3. Patients with complications involving the heart, liver, and kidney; patients with functional impairment or other diseases such as serious infections, tumors, nervous system disorders, immune system disorders, mental disease, etc.;
4. Patients with complications involving the digestive system and/or eating disorders;
5. Patients on sex hormone or vitamin D supplements, glucocorticoids, and other drugs;
6. Patients with no autonomous activity, low cognitive function, or those who are unable to cooperate;
7. Patients with significant weight loss (>5% of their body weight) within the last 3 months;
8. Patients who refused to sign the informed consent form;

General Data Collection

1. General information on the patients were collected from the Department of Endocrinology, the Second Affiliated Hospital of Anhui Medical University database; these included gender, age, occupation, history of smoking and alcohol consumption, etc., as well as detailed medical records on when the patient developed T2DM and the course of the disease as well as the chronic issues and complications caused by T2DM.
2. Information on fasting blood glucose levels (after fasting for >10 h), systolic blood pressure (SBP), diastolic blood pressure (DBP), height, weight, and BMI were also collected.

Laboratory Testing

Venous blood and morning urine were collected after 10 h of overnight fasting and the fasting blood glucose (FBG) and triglyceride (TG) levels were measured using a Beckman Coulter (AU5831) automatic biochemical analyzer. The total cholesterol (TCH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA), albumin (ALB), and urine creatinine (urine creatinine) levels were also determined with Beckman Coulter (AU5831). The hemoglobin A1c (HbA1c) levels were measured using an Arco lay hemoglobin analyzer HA-8180. The hemoglobin (Hb) levels were measured using a hemoglobin analyzer XN (Sysmex, XN). An automatic Seamless protein analyzer BNII was used to detect the presence of albumin in urine samples, and the urine albumin to creatinine ratio (UACR) was calculated. A fully automated chemiluminescent immunoassay IMMULITE 2000XPi (Seamless, IMMULITE 2000XPi) was used to measure the levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), testosterone (TES) and estradiol (E2) levels in blood were tested using another automatic chemiluminescence analyzer (Cobas e801, Roche). Levels of vitamin D (25-Hydroxy vitamin D or 25(OH)D) were measured using the electrochemiluminescence analyzer, Cobas e602 (Roche).

All laboratory tests and measurements were conducted at the clinical laboratory of the Second Affiliated Hospital of Anhui Medical University.

The estimated glomerular filtration rate (eGFR) was estimated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula:[11]

$$\mathrm{eGFR}\left(\mathrm{ml/min} \bullet 1.73\mathrm{m}^2\right) = \mathrm{a} \times (\mathrm{Scr/b})^{\mathrm{c}} \times 0.993^{\mathrm{Age}}$$

(Note: a value: women are 144, men are 141. b value: women are 0.7, men are 0.9. c values were used according to gender and serum creatinine. For women, Scr≤0.7mg/dl, c=−0.329, Scr>0.7mg/dl, c=−1.209; For men, Scr≤0.9mg/dl, c=−0.411, Scr>0.9mg/dl, c=−1.209. Scr: 1mg/ dl=88.4umol/L).

Muscle Function and Strength Measurements

The grip strength and walking speed of all subjects were measured by trained medical staff. Electronic hand dynamometer was used to measure the grip strength of the subjects. The time required for the subjects to complete a distance of 6 m at their usual speed was measured and the walking speed was calculated.

Measurement of Body Composition

A LUNAR Prodigy dual-energy X-ray absorptiometry (DXA) detector (GE) was used to measure the mass of fat and muscle tissues in the whole body, trunk, upper limbs and lower limbs; the bone mineral densities (BMD) of the left femoral neck, Ward's triangle, greater trochanter, and lumbar spines L1-4 were also measured.

The skeletal muscle mass of four limbs = muscle mass of two upper limbs + muscle mass of two lower limbs was used to calculate the ASMI.

$$\mathrm{ASMI} = \text{limb skeletal muscle mass}\,(\mathrm{kg})/\mathrm{height}^2(\mathrm{m})^2$$

Statistical Analyses

This study was conducted as a cross-sectional observational study. Its sample size estimation formula is presented in Eq. below:

$$n = (\frac{Z1 - \alpha/2}{\delta})^2 \times p \times (1 - p)$$

where $Z_{1-\alpha/2} = 1.96$, δ represents the allowable error (0.05), and P represents the predicted prevalence.[12] According to the literature review, the predicted prevalence of sarcopenia in patients with diabetes is 20%. Therefore, the sample size was calculated as n = $(1.96/0.05)^2$ * 0.2 * (1-0.2) = 246. To reduce the influence of sampling errors on the results, a total of 334 subjects were recruited.

Data analysis was done using the SPSS (v. 26.0) software. The measurement data were tested using the Kolmogorov–Smirnov (KS) test to check if the data were normally distributed. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and independent sample *t*-tests were used for comparisons between groups. Non-normally distributed data were expressed as median with interquartile spacing M (P_{25}, P_{75}) and the Wilcoxon rank sum test was used for comparisons between groups. Percentages (%) were used for enumeration data and Chi-square (χ^2) tests or Fisher exact tests were used for comparisons between groups. Multivariate analysis was performed by the binary logistic regression. The diagnostic ability of each factor was calculated by receiver operating characteristic curve (ROC). For all statistical tests, P <0.05 indicates statistical significance.

Results

Prevalence of Sarcopenia in Hospitalized Patients with T2DM

Among the 334 hospitalized patients with T2DM that were included in this study, the overall prevalence of sarcopenia was 30.2% (101/334). The prevalence of sarcopenia was 41.3% (66/160) in men and 20.1% (35/174) in women, which indicates that sarcopenia is significantly more prevalent in men with T2DM than in women with T2DM (P<0.05).

Comparison of Clinical Data Between the Two Groups

There were no significant differences in age, diabetes course, SBP, DBP, FBG, HbA1c, Hb, Alb, TCH, LCLC, HDL, eGFR, UA, urinary ACR, and GH between the two groups (P>0.05). The values of BMI and serum levels of TG, 25(OH)D, and IGF-1 were significantly higher in the patients in the sarcopenia group than those in the patients in the non-sarcopenia group (P<0.05). The SCr levels in the patients in the sarcopenia group were significantly higher than those for the patients in the non-sarcopenia group (P<0.05; Table 1).

Multivariate Logistic Regression Analysis of T2DM Patients with Sarcopenia

By using the presence of sarcopenia as the dependent variable and gender, BMI value, and serum levels of TG, SCr, 25(OH)D, and IGF-1 as the independent variables, a multifactorial logistic regression analysis was conducted. The results showed that gender (specifically for men; OR=4.997, 95% CI: 2.611–9.564), low BMI (OR=1.525, 95% CI: 1.353–1.718), low levels of 25 (OH)D (OR=1.076, 95% CI:1.036–1.117), and low levels of IGF-1 (OR=1.013, 95% CI: 1.006–1.020) were independent risk factors of sarcopenia in patients with T2DM (P<0.05; Table 2).

Comparison of Clinical Data of Men with T2DM Between the Two Groups

Among the 160 men patients with T2DM, there were no statistically significant differences in age, duration of diabetes, and levels of SBP, DBP, FBG, HbA1c, Hb, Alb, TG, TCH, LCLC, SCr, eGFR, UA, urinary ACR, and GH between those in the sarcopenia group and those in the non-sarcopenia group (P>0.05). The BMI values and serum levels of 25(OH)D, IGF-1, and testosterone in the patients in the sarcopenia group were significantly lower than those for patients in the non-sarcopenia group (P<0.05). The levels of serum HDL in the patients in the sarcopenia group were significantly higher than those for patients in the non-sarcopenia group (P<0.05; Table 3).

Multivariate Logistic Regression Analysis of Men with T2DM and Sarcopenia

When the presence or absence of sarcopenia was used as a dependent variable with BMI values and serum levels of HDL, 25(OH)D, IGF-1, and testosterone were used as independent variables, the multivariate logistic regression analysis showed that low BMI (OR=1.809, 95% CI: 1.465–2.235), low levels of 25(OH)D (OR=1.071, 95% CI:1.012–1.133), low

Table 1 Comparison of Clinical Data Between Sarcopenia and Non-Sarcopenia Groups

	Sarcopenia Groups (n=101)	Non-Sarcopenia group (n=233)	Z/t value	P value
Age (y)	68.15±5.60	68.21±5.48	0.100	0.921
Course of disease (y)	10 (6, 18)	10 (6, 17)	0.211	0.833
BMI (kg/m^2)	22.52±2.47	25.28±3.17	8.587	< 0.001
SBP (mmHg)	133.24±17.35	136.41±17.26	1.541	0.124
DBP (mmHg)	73.91±9.58	74.51±10.35	0.494	0.622
FBG (mmo/l)	8.19±3.42	8.08±2.90	0.315	0.753
HbA1c (%)	9.06±1.93	8.74±1.92	1.409	0.160
Hb (g/l)	125.61±21.8	126.72±19.41	0.459	0.646
Alb (g/l)	37.96±5.2	40.15±23.22	0.936	0.350
TG (mmo/l)	1.25 (0.89, 1.71)	1.46 (0.97, 2.06)	2.592	0.010
TCH (mmo/l)	4.27±1.16	4.46±1.22	1.324	0.186
LDL-C (mmo/l)	2.64±0.9	2.73±0.82	0.870	0.385
HDL (mmo/l)	1.16±0.28	1.13±0.28	0.953	0.341
SCr (umol/l)	71 (57.5, 90.5)	64 (52, 82)	2.237	0.025
eGFR [mL/(min · 1.73m2)]	82.07±21.57	84.76±19.86	1.109	0.268
UA (umol/l)	314.97±94.39	306.94±93.33	0.719	0.472
Urine ACR (mg/g)	19.78 (11.96, 60.07)	24.58 (13.81, 65.89)	1.497	0.134
25(OH)D (ng/mL)	27.15±7.81	30.93±8.31	3.891	< 0.001
GH (ng/mL)	2.03 (0.81, 2.80)	2.01 (0.55, 2.78)	0.644	0.520
IGF-1 (ng/mL)	139.61±43.80	156.58±40.43	3.328	0.001

Table 2 Multivariate Logistic Regression Analysis of Sarcopenia in Patients with T2DM

	B	SE	Walds	P-value	OR value (95%)
Gender	1.609	0.331	23.597	< 0.001	4.997 (2.611, 9.564)
BMI	0.422	0.061	47.808	< 0.001	1.525 (1.353, 1.718)
TG	0.130	0.122	1.135	0.287	1.139 (0.896, 1.447)
SCr	0.005	0.005	1.045	0.307	0.995 (0.986, 1.004)
25(OH)D	0.073	0.019	14.354	< 0.001	1.076 (1.036, 1.117)
IGF-1	0.013	0.004	13.556	< 0.001	1.013 (1.006, 1.020)

levels of IGF-1 (OR=1.011, 95% CI: 1.000–1.021) and low levels of testosterone (OR=1.003, 95% CI: 1.000–1.006) were independent risk factors of sarcopenia in men with T2DM (P<0.05; Table 4).

Comparison of Clinical Data of Women T2DM Patients Between the Two Groups

Among the 174 women with T2DM, there were no significant differences in age, duration of diabetes, SBP, DBP, FBG, HbA1c, Hb, Alb, TG, HDL, SCr, eGFR, UA, urinary ACR, and GH levels between those in the sarcopenia group and those in the non-sarcopenia group (P>0.05). The BMI values, and serum levels of TCH, LDL-C, 25(OH)D, IGF-1, and estradiol in the patients in the sarcopenia group were significantly lower than those in the patients in the non-sarcopenia group (P<0.05; Table 5).

Multivariate Logistic Regression Analysis of Women with T2DM and Sarcopenia

When the presence of sarcopenia was used as the dependent variable with the BMI values and serum levels of TCH, LDL-C, 25(OH)D, IGF-1, and estradiol as the independent variables, the multifactorial logistic regression analysis showed that low BMI (OR=1.357, 95% CI: 1.159–1.588), low levels of 25(OH)D (OR=1.064, 95% CI: 1.007–1.124),

Table 3 The Clinical Data of Men T2DM Patients Were Compared Between the Two Groups

	Sarcopenia Group (n=66)	Non-Sarcopenia Group (n=94)	Z/t value	P value
Age (y)	67.97±5.74	67.55±5.39	0.468	0.640
Course of disease (y)	10 (6, 18)	10 (6, 19)	0.322	0.747
BMI (kg/m^2)	22.69±2.23	26.03±2.67	8.346	< 0.001
SBP (mmHg)	134.11±19.00	136.54±16.73	0.857	0.393
DBP (mmHg)	74.27±10.21	75.77±11.09	0.866	0.388
FBG (mmo/l)	8.08±3.25	8.02±2.70	0.127	0.899
HbA1c (%)	9.02±1.98	8.70±1.79	1.075	0.284
Hb (g/l)	130.97±20.98	136.35±20.25	1.630	0.105
Alb (g/l)	37.64±5.54	38.86±4.06	1.611	0.109
TG (mmol/l)	1.2 (0.85, 1.71)	1.425 (0.915, 1.74)	1.160	0.246
TCH (mmol/l)	4.32±1.03	4.16±1.17	0.880	0.380
LDL-C (mmol/l)	2.7±0.85	2.55±0.84	1.105	0.271
HDL (mmol/l)	1.15±0.27	1.06±0.27	2.084	0.039
SCr (umol/l)	88.59±40.21	80.1±24.8	1.525	0.130
eGFR [mL/(min · 1.73m2)]	80.69±22.79	85±17.96	1.335	0.184
UA (umol/l)	330.61±94.49	330±77.63	0.044	0.965
Urine ACR (mg/g)	17.28 (11.78, 41.25)	20.94 (13.25, 70.62)	0.842	0.400
25(OH)D (ng/mL)	27.49±7.57	30.86±8.07	2.671	0.008
GH (ng/mL)	2.11 (1.00, 2.78)	2.29 (0.61, 2.77)	0.052	0.959
IGF-1 (ng/mL)	145.69±40.1	163.79±39.98	2.816	0.005
Testosterone (ng/dl)	353.05±127.24	448.93±166.84	3.933	< 0.001

Table 4 Multivariate Logistic Regression Analysis of Sarcopenia in Men Patients with T2DM

	B	SE	Walds	P-value	OR value (95%)
BMI	0.593	0.108	30.285	< 0.001	1.809 (1.465, 2.235)
HDL	0.371	0.870	0.181	0.670	1.449 (0.263, 7.977)
25 (OH) D	0.069	0.029	5.712	0.017	1.071 (1.012, 1.133)
IGF-1	0.011	0.005	4.126	0.042	1.011 (1.000, 1.021)
Testosterone	0.003	0.002	5.061	0.024	1.003 (1.000, 1.006)

and low levels of IGF-1 (OR=1.014, 95% CI: 1.003–1.024) were independent risk factors of sarcopenia in women with T2DM (P<0.05; Table 6).

ROC Curve Evaluated the Diagnostic Value of Related Factors

ROC curve analysis showed that the area under the curve of BMI, 25(OH) D and IGF-1 for the diagnosis of sarcopenia in the general population was 0.76, 0.617 and 0.610, the sensitivity was 60.9%, 63.1% and 84.5%, and the specificity was 83.2%, 58.4% and 38.6%, respectively, all P < 0.05. The combined factors of BMI, 25 (OH) D and IGF-1 had an area under the curve of 0.848, sensitivity of 77.7% and specificity of 80.2% (P < 0.05; Table 7, Figure 1A).

In men patients, the area under the curve of BMI, 25 (OH) D, IGF-1 and testosterone for the diagnosis of sarcopenia was 0.84, 0.612, 0.629 and 0.668, and the sensitivity was 78.7%, 67.0%, 76.6% and 78.7%, respectively. The specificity was 80.3%, 57.6%, 48.5% and 53.0%, respectively, all P < 0.05. The combined factors of BMI, 25 (OH) D, IGF-1 and testosterone had an area under the curve of 0.882, sensitivity of 84.0% and specificity of 83.3% (P < 0.05; Table 8, Figure 1B).

Table 5 The Clinical Data of Women T2DM Patients Were Compared Between the Two Groups

	Sarcopenia Group (n=35)	Non-Sarcopenia Group (n=139)	Z/t value	P value
Age (y)	68.49±5.41	68.66±5.51	0.170	0.865
Course of disease (y)	10 (5, 18)	10 (4, 17)	0.522	0.601
BMI (kg/m^2)	22.19±2.87	24.77± 3.39	4.132	<0.001
SBP (mmHg)	131.6±13.8	136.32±17.68	1.471	0.143
DBP (mmHg)	73.23±8.36	73.65±9.76	0.237	0.813
FBG (mmo/l)	8.41±3.76	8.12±3.04	0.483	0.630
HbA1c (%)	9.13±1.88	8.76±2.01	0.977	0.330
Hb (g/l)	115.51±19.87	120.2±15.84	1.483	0.140
Alb (g/l)	38.57±4.49	41.02±29.89	0.483	0.630
TG (mmol/l)	1.31 (0.91, 1.71)	1.56 (1.02, 2.16)	1.825	0.068
TCH (mmol/l)	4.17±1.37	4.66±1.22	2.057	0.041
LDL-C (mmol/l)	2.59 (1.69, 2.99)	2.70 (2.26, 3.26)	2.045	0.041
HDL (mmol/l)	1.17±0.31	1.17±0.27	0.007	0.994
SCr (umol/l)	62.83±22.29	65.23±33.59	0.401	0.689
eGFR [mL/(min · 1.73m2)]	84.66±19.08	84.60±21.1	0.017	0.987
UA (umol/l)	285.49±88.11	291.35±99.88	0.318	0.751
Urine ACR (mg/g)	26.94 (15.39, 110.77)	28.33 (15.97, 59.69)	0.473	0.636
25(OH)D (ng/mL)	26.51±8.31	30.98±8.50	2.793	0.006
GH (ng/mL)	1.98 (0.38, 2.95)	1.78 (0.38, 2.78)	0.332	0.740
IGF-1 (ng/mL)	128.16±48.58	151.71±40.13	2.649	0.011
Estradiol (pmol/l)	39.39 (24.66, 67.63)	59.20 (31.62, 112.34)	2.395	0.017

Table 6 Multivariate Logistic Regression Analysis of Sarcopenia in Women Patients with T2DM

	B	SE	Walds	P-value	OR value (95%)
BMI	0.305	0.080	14.382	< 0.001	1.357 (1.159, 1.588)
TCH	0.315	0.396	0.633	0.426	1.371 (0.630, 2.980)
LDL-C	0.069	0.611	0.013	0.910	1.072 (0.324, 3.549)
25(OH)D	0.062	0.028	4.809	0.028	1.064 (1.007, 1.124)
IGF-1	0.014	0.005	6.570	0.010	1.014 (1.003, 1.024)
Estradiol	0.008	0.004	3.334	0.068	1.008 (0.999, 1.017)

Table 7 ROC Curve Analysis of Sarcopenia by Total Population Correlation Factors

	AUC (95%CI)	SE	P-value	Walds	Sensitivity	Specificity	Youden Index
BMI	0.756 (0.703, 0.809)	0.027	<0.001	24.49	60.9%	83.2%	0.441
25(OH)D	0.617 (0.554, 0.681)	0.032	0.001	28.09	63.1%	58.4%	0.215
IGF-1	0.610 (0.542, 0.678)	0.035	0.001	112.94	84.5%	38.6%	0.231
Combined analysis	0.848 (0.804, 0.893)	0.023	<0.001	0.71	77.7%	80.2%	0.579

In women patients, the area under the curve of BMI, 25 (OH) D and IGF-1 for the diagnosis of sarcopenia was 0.721, 0.630 and 0.650, the sensitivity was 61.9%, 33.8% and 82.7%, and the specificity was 80.0%, 88.6% and 54.3%, respectively, all $P < 0.05$. The combined factors of BMI, 25 (OH) D and IGF-1 had an area under the curve of 0.809, sensitivity of 86.3% and specificity of 74.3% ($P < 0.05$; Table 9, Figure 1C).

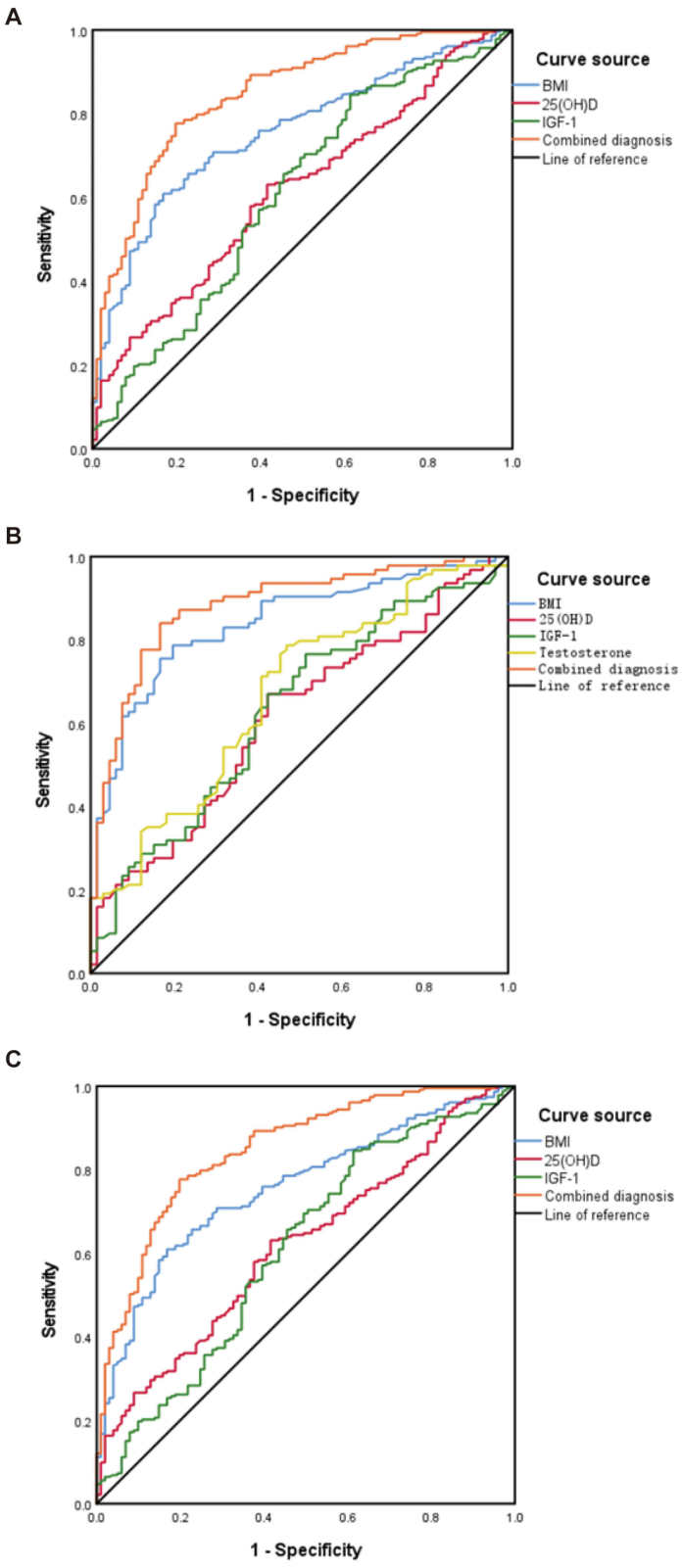

Figure 1 Flow chart of the diagnosis of sarcopenia. (**A**) ROC curve of total population-related factors for sarcopenia. (**B**) ROC curve of men correlation factors for sarcopenia. (**C**) ROC curve of women correlation factors for sarcopenia.

Table 8 ROC Curve Analysis of Men Correlation Factors for Sarcopenia

	AUC (95%CI)	SE	P-value	Walds	Sensitivity	Specificity	Youden Index
BMI	0.840 (0.779, 0.902)	0.031	<0.001	24.36	78.7%	80.3%	0.590
25(OH)D	0.612 (0.524, 0.700)	0.045	0.016	27.89	67.0%	57.6%	0.246
IGF-1	0.629 (0.542, 0.717)	0.045	0.005	145.78	76.6%	48.5%	0.251
Testosterone	0.668 (0.583, 0.752)	0.043	<0.001	338	78.7%	53.0%	0.317
Combined analysis	0.882 (0.829, 0.936)	0.027	<0.001	0.56	84.0%	83.3%	0.673

Table 9 ROC Curve Analysis of Women Correlation Factors for Sarcopenia

	AUC (95%CI)	SE	P-value	Walds	Sensitivity	Specificity	Youden index
BMI	0.721 (0.631, 0.811)	0.046	<0.001	23.77	61.9%	80.0%	0.419
25(OH)D	0.630 (0.532, 0.728)	0.050	0.018	34.91	33.8%	88.6%	0.224
IGF-1	0.650 (0.534, 0.766)	0.059	0.006	112.94	82.7%	54.3%	0.370
Combined analysis	0.809 (0.728, 0.891)	0.042	<0.001	0.79	76.3%	74.3%	0.506

Discussion

Sarcopenia is a condition characterized by the loss of skeletal muscle function and mass associated with ageing. Recent studies have found that the prevalence of sarcopenia in patients with T2DM has increased significantly by years; however, the severity of the disease can be quite variable. In this study, the incidence and risk factors of sarcopenia in patients with T2DM were assessed using the AWGS criteria.

In recent years, many Asian studies have reported prevalence rates of sarcopenia ranging from 8.3% to 28.8%.[4,13–16] A recent review used data from 28 studies to conduct a meta-analysis on the prevalence of sarcopenia. The results showed that 18% of the patients with T2DM also suffer from sarcopenia.[17] A Malaysian study on patients with T2DM found that the prevalence of sarcopenia in this population was 28.5%; this result is similar to the age of the patients and the prevalence of sarcopenia found in our work.[18] In this study, a total of 334 hospitalized patients with T2DM (mean age = 68.19±5.5 years) were included in this study, of which 101 were diagnosed with sarcopenia. This indicates an overall prevalence of 30.2%, which is higher than that of most other studies. The reason for this may be because this study was focused on T2DM patients who were hospitalized; therefore, the overall prevalence of T2D-associated complications and concomitant diseases were likely to be higher in this population than those of the general T2DM population in the community. In addition, it is possible that in this study, the race, sex ratio, ages, and BMI values of the subjects selected and the methods used for diagnosing sarcopenia may be different from those of other studies, which is reflected in the different prevalence values obtained here.

The effect of gender on the prevalence of sarcopenia in patients with T2DM has been variable in different studies. Most studies have shown that the prevalence of sarcopenia in men with T2DM is higher.[19–21] However, others have shown that the prevalence of sarcopenia in women with T2DM is higher.[22,23] In this study, the prevalence of sarcopenia in men with T2DM was 41.3%, which was significantly higher than that in women with T2DM (20.1%; P<0.05). Overall, our study shows that gender is an independent risk factor of sarcopenia in T2DM patients and that men with T2DM are more likely to develop sarcopenia than women with T2DM.

In this study, we find that a decrease in the testosterone level was an independent risk factor of sarcopenia in men with T2DM. Reduced testosterone levels can affect the structure and function of muscling, especially in the skeletal muscle at the distal extremities.[24] Testosterone therapy can promote muscle growth, increase the amount of lean tissue, and improve the muscle strength and function of lower limbs.[25,26] In addition, a 2018 study has found that patients with sarcopenia have elevated levels of IL-6, suggesting that changes in the sex hormone levels in older patients with sarcopenia may influence inflammatory cytokine expression.[27]

In women with T2DM, however, the serum estrogen level was not an independent risk factor of sarcopenia; however, women diagnosed with sarcopenia did have significantly lower levels of estradiol than those without sarcopenia. The relationship between estrogen and sarcopenia in human studies remains controversial. Zacarias-Flores et al[28] showed that

the increase in oxidative stress in early post menopause women was linked to decreases in muscle mass. Pollanen et al[29] have found that estrogen levels in muscle tissue were correlated with muscle mass and function. However, one study on ageing has shown that estrogen levels are not associated with muscle mass or strength in older women and several studies on estrogen replacement therapy have been inconsistent.[30–32]

The BMI values of patients with T2DM in the sarcopenia group were lower than those of patients with T2DM in the non-sarcopenia group. In addition, low BMI was an independent risk factor of sarcopenia in patients with T2DM. In recent years, multiple studies have shown that T2DM patients with sarcopenia have significantly lower BMI values than T2DM patients without sarcopenia; in addition, the prevalence of sarcopenia is significantly lowered as BMI increases.[7,33,34] The results of our study are consistent with those of these previous studies. A study has found that patients with T2DM have obvious muscle decay. The degree of muscle decay increases also with increasing BMI and is independently correlated with muscle strength and muscle mass.[35] Therefore, keeping BMI values within the appropriate range and avoiding excessive emaciation or obesity in patients with T2DM is necessary for maintaining muscle content, muscle function status, and reducing the sarcopenia.

Recent studies have found that vitamin D is also involved in important pathophysiological processes related to muscles by affecting skeletal muscle metabolism and function.[36] Vitamin D maintains the normal contractile function of skeletal muscle by stabilizing calcium and phosphorus metabolism in skeletal muscle. Vitamin D can also regulate glucose and lipid metabolism in multiple insulin-sensitive tissues such as adipose tissues, skeletal muscle, liver, and pancreas,[37] and participate in skeletal muscle metabolism by affecting the supply of fatty acids to skeletal muscle; therefore, vitamin D levels can affect the sarcopenia. Hirani,[38] who conducted a follow-up study on 1705 Australian men, found that the incidence of sarcopenia was 3.9% during the 2nd year of the follow-up and 8.6% during the 5th year of the follow-up; the study also found that a low baseline vitamin D level was independently associated with the incidence of sarcopenia. In this study, the vitamin D levels in the patients in the sarcopenia group were lower than those of patients in the non-sarcopenia group. Overall, it is clear that a low vitamin D level was an independent risk factor of sarcopenia in patients with T2DM.

An important regulator of muscle and bone growth whose levels are significantly reduced in the population is IGF-1. A study on 1292 people has shown that decreased IGF-1 levels in people were associated with decreased grip strength and poor physical activity.[39] A multi-center prospective study led by the Peking Union Medical College Hospital in China has shown that the higher levels of IGF-1 are associated with a reduced risk of developing sarcopenia and the IGF-1 levels are significantly and positively correlated with muscle mass and muscle strength in limbs.[40] In this study, we find that IGF-1 levels in the patients in the sarcopenia group were lower than those for patients in the non-sarcopenia group and that a lower IGF-1 level in either men or women was an independent risk factor of sarcopenia in T2DM patients.

ROC curve analysis results showed that BMI, 25 (OH) D, IGF-1, and testosterone (for men) had predictive significance for sarcopenia with T2DM ($P < 0.05$). However, the AUC of 25 (OH) D, IGF-1 and testosterone predictors of sarcopenia were all <0.7, while the AUC of BMI and the combined measures of these factors were all >0.7 (AUC of BMI: 0.76 in the general population, 0.84 in men, and 0.721 in women; The AUC of the combined factors: 0.848 for the total population, 0.882 for men, 0.809 for women), has great predictive significance.

This study is a single-center study with a small sample size and may suffer from selectivity bias. As this is a cross-sectional study, it is not possible to establish a causal relationship between sarcopenia and the factors associated with sarcopenia. Another limitation of this study is that it only focuses on T2DM patients; patients without T2DM were not included as a control group. Therefore, more rigorous, more comprehensive, prospective, and multi-center, studies of larger sample sizes need to be designed for further verification of our results. This study could be useful in the prevention and treatment of sarcopenia in patients with T2DM.

Conclusions

In summary, the prevalence of sarcopenia has increased in hospitalized patients with T2DM. Gender, low BMI, low serum vitamin D levels and low serum IGF-1 levels are risk factors of sarcopenia in patients with T2DM. Low BMI, 25 (OH)D, IGF-1, and testosterone (for men) all contributed to the prediction of sarcopenia, among which BMI and combined factors were more significant. The findings are the clinical utility of certain novel risk factors for the association of sarcopenia in T2DM.

Data Sharing Statement

The data sets generated for this study are available on request to the corresponding author.

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Disclosure

The authors declare no conflicts of interest in this work.

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