# Soluble interleukin 2 receptor is risk for sarcopenia in Men with high fracture risk

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## ARTICLE INFO

## ABSTRACT

*Background & aims:* Sarcopenia is an age-related disease that increases the risk of falls and fractures in older adults. However, there is no blood biochemical marker to help to predict or diagnose sarcopenia in clinical practice. Soluble interleukin 2 receptor (sIL-2R) was reported to be associated with muscle satellite cell dysfunction which played an important role in the pathogenesis of sarcopenia. Thereby, we aimed to explore the association between serum sIL-2R and sarcopenia in older adults at high risk of fractures.

*Methods:* A total of 429 hospitalized older adults (age ≥55 years) were enrolled in this cross-sectional study (mean age = 66.62 ± 6.59 years; 62.7% female). Logistic regression analysis was performed to assess the association of sIL-2R with sarcopenia, muscle mass, muscle strength, and physical performance, respectively. The optimal models for the diagnosis of sarcopenia and low hand grip strength (HGS) were established by multivariable binary logistic regression analysis with backward selection, and further were evaluated for the diagnostic values by receiver operating characteristic (ROC) curve.

*Results:* Higher sIL-2R levels were found in sarcopenia than no-sarcopenia group in male (median 421 U/mL (interquartile range [IQR] 217 U/mL) vs median 362 U/mL (IQR 157 U/mL); n = 77 vs 83; $p < 0.01$). Compared to the lowest sIL-2R tertile, the highest tertile of sIL-2R was independently associated with the risk of low HGS (odds ratio [OR] 4.608, 95% confidence interval [CI] 1.673–12.695) and the risk of sarcopenia (OR 3.306, 95% CI 1.496–7.302) in men. ROC curves revealed that the Area Under the Curve (AUC) of the optimal models for diagnosing sarcopenia and low HGS was 0.752 and 0.846.

*Conclusion:* Our results suggest that serum sIL-2R is the independent risk factor for sarcopenia and low muscle strength only in men. sIL-2R may be developed to be a biochemical marker for sarcopenia and low muscle strength diagnoses in older men at high risk of fractures, but more prospective studies are needed to prove it.

*The translational potential of this article:* Our results showed that the highest tertile of sIL-2R was independent of low risk of HGS and sarcopenia in men, compared to the lowest tertile. As the population ages, sIL-2R may become a potential diagnostic tool for predicting low HGS and sarcopenia among men at high risk of fractures.

## 1. Introduction

With the aging of the population, the incidence of osteoporosis, a senile disease, and osteoporosis fracture, the diseases' greatest hazard, is increasing annually. However, clinical antiosteoporotic therapy can only lower the incidence of osteoporotic hip fractures by less than 67% [1–3]. This is because decreased biomechanical strength of bone in osteoporosis is only one of the risk factors for fracture, but there is another important factor—sarcopenia, an age-related disease characterized by loss of muscle mass, muscle strength and physical performance, leading to increased risks of falls [4]. In Asian countries, the prevalence of sarcopenia has gone up to a high level [5] ranging from 5.5% to 25.7% [6].

Due to a shortage of equipment to measure muscle mass [7] (dual-energy X-ray absorptiometry, bioimpedance, computed tomography or medical magnetic resonance imaging equipment) and grip strength (dynamometer) in many primary hospitals, the diagnosis of sarcopenia

remains difficult to execute [6]. Therefore, it is essential to find new methods for the diagnosis of sarcopenia.

Interleukin 2 receptor (IL-2R) is a kind of receptor complexes and can be sloughed off from the cell membrane into serum (called soluble IL-2 receptor, sIL-2R). In clinical, sIL-2R was commonly employed as an inflammation indicator which was found elevated in a variety of muscle-associated diseases, such as multiple sclerosis and thyrotoxic myopathy [8–11]. Recent animal and in vitro studies also suggested that IL-2R, with which sIL-2R competitively acted [12,13], was involved in muscle satellite cell proliferation and migration [14,15]. Inflammation and satellite cell dysfunction were reported to cause muscle atrophy and a predisposition to sarcopenia [12,13,16–18]. Thereby it is plausible that sIL-2R is involved in sarcopenia.

However, there were few clinical studies on the relationship between sarcopenia and sIL-2R. In this study, we aimed to analyze the association of sIL-2R with sarcopenia and evaluate the diagnostic value of sIL-2R for sarcopenia in population at high risk of osteoporotic fractures.

## 2. Materials and methods

### 2.1. Study design and participants

We performed a retrospective study evaluating the patients admitted to Department of Endocrinology and Metabolism, Shanghai Tenth People's Hospital, from November 2020 to December 2021. Patients aged ≥55 years and satisfied any of the following criteria are eligible to participate in this study (with high fracture risk): 1) Current or past hip or vertebral osteoporotic fracture; 2) T-score ≤ −2.5 and at least one risk factor is present (risk factors include the following: a. History of hip or non-vertebral fractures; b. History of parental hip fractures in the family; c. Age ≥65 years; d. Low body mass index (BMI <18.5 kg/m$^2$); e. Current smoking; 3) No fracture occurred, and the T-score < −3; 4) The fracture risk assessment tool recommended by the World Health Organization predicts the probability of a hip fracture ≥3% or a major site fracture ≥20% within ten years. Exclusion criteria were as follows: 1) severe organ failure (heart failure, renal failure, respiratory failure, or liver failure); 2) severe systemic diseases (hematological disorder, systemic connective tissue disease, malignant tumors); 3) acute infectious disease; 4) mental illness or physical disability; 5) use of drugs that may affect muscle (glucocorticoids or immunosuppressive drugs); 6) data of hand grip strength (HGS), gait speed, five chair stand test (FCST) and appendicular skeletal muscle mass index (ASMI) unavailable; 7) serum sIL-2R data unavailable. The diseases were jointly diagnosed by two experienced clinicians. This research was approved by the ethics committee of Shanghai Tenth People's Hospital and the requirement for informed consent was waived due to the retrospective design of the study.

### 2.2. Sarcopenia assessments

The diagnosis of sarcopenia was based on Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment [6].

Muscle mass was measured by dual-energy x-ray absorptiometry (DXA) Hologic scanner (Hologic Discovery QDR Series, Bedford, MA, USA), and ASMI (ratio of appendicular muscle mass to squared height) less than 7.0 kg/m$^2$ in male or 5.4 kg/m$^2$ in female was defined as low muscle mass.

Hand grip strength was assessed with digital dynamometer (CAMRY EH10, Xiangshan, Guangdong), and HGS less than 28 kg in male or 18 kg in female was defined as low muscle strength.

Physical performance was evaluated by 6-m gait speed test and five chair stand test. It was 6-m gait speed test time more than 6 s (low gait speed) or FCST time no less than 12 s (low FCST) that was defined as low physical performance.

### 2.3. Patients' information and laboratory tests

Medical records including age, sex, height, weight, body mass index (BMI), nutrition and exercise state, history of diseases, and history of smoking and alcohol were collected. Nutrition state was evaluated based on Controlling Nutritional Status (CONUT) Score and was divided into four levels: normal (0–1 points), mild (2–4 points), mid (5–8 points) and severe (>8 points) [19]. Exercise state was assessed using metabolic equivalent (MET) calculated according to the following formula: MET coefficient of activity × duration (hours) × frequency (days per week). Activities were divided into four levels, including sitting, walking, moderate activity, and vigorous activity, corresponding to MET coefficients of 1.0, 3.3, 4.0 and 8.0, respectively [20].

After 8 h of fasting, all participants' blood samples were obtained in the early morning of the day after their admission, and then forwarded to the clinical laboratory of our hospital. Laboratory parameters including peripheral blood cell indexes (white blood cell, platelets, neutrophils, lymphocyte, monocyte), inflammation indexes (interleukin 2 (IL-2), interleukin 6 (IL-6), interleukin 8 (IL-8), serum amyloid A (SAA)), hepatic function indexes (alanine aminotransferase (ALT), aspartate aminotransferase (AST)), renal function indexes (creatinine, uric acid), lipid metabolism related indexes (total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL)) and glycosylated hemoglobin (HbA1c) were measured. In addition, sIL-2R was measured in serum using sandwich enzyme-linked immunoassay according to the manufacturers' test instructions (Glyn Rhonwy, United), and the lowest detection limit was 5U/mL.

### 2.4. Statistical methods

Continuous variables were presented as the mean ± standard deviation (SD) or median (interquartile range, IQR) and categorical variables as absolute and relative frequencies. The statistical significance of differences between two independent samples was evaluated using independent two-sample t-test or Mann-Whiney U-test for continuous variables and Chi-square test for categorical variables. Spearman's correlation analysis was performed to assess the correlation of sIL-2R (logarithm-transformed) with HGS, Gait Speed, FCST, and ASMI. Furthermore, multivariable binary logistic regression analysis was performed to identify the independent association of sarcopenia with sIL-2R tertiles with odds ratios (OR) and 95% confidence intervals (CIs) calculated, in which we adjusted for confounders based on literature and expert knowledge. Finally, we established optimal models for sarcopenia and low HGS using multivariable binary logistic regression analysis with backward selection. And receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic values of the optimal models. Statistical analysis was conducted in SPSS 20.0. In all analyses, *p* value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics of the study participants

515 inpatients were assessed for their eligibility for inclusion and 86 patients were excluded based on exclusion criteria. As a result, a total of 429 patients (269 females and 160 males) were included in the study. The baseline characteristics were summarized in Table 1 and Table S1. The mean age of all participants was 66.62 ± 6.59 years. Of them, 129 women and 77 men were classified as sarcopenia, 140 women and 83 men as no-sarcopenia. The comparison of baseline characteristic between sarcopenia and no-sarcopenia disaggregated by sex. In men, patients with sarcopenia had higher age, creatinine, total body fat and prevalence of coronary heart disease than those without. And in women, sarcopenia presented a higher age and a lower MET. There were no differences in

**Table 1**
Comparison of baseline characteristics between sarcopenia and no-sarcopenia patients.

| | All (n = 429) | | Male (n = 160) | | Female (n = 269) | |
|---|---|---|---|---|---|---|
| | No-sarcopenia | Sarcopenia | No-sarcopenia | Sarcopenia | No-sarcopenia | Sarcopenia |
| | n = 223 | n = 206 | n = 83 | n = 77 | n = 140 | n = 129 |
| Age (years) | 65 (9) | 69 (10) *** | 63 (8) | 68 (11) *** | 65 (8) | 69 (9) *** |
| BMI (kg/m$^2$) | 24.57 (4.86) | 24 (3.94) * | 24.62 (4.03) | 24.3 (3.84) | 24.27 (5.03) | 23.79 (4.14) |
| White Blood Cell (10$^9$/L) | 5.84 (2.15) | 5.69 (1.64) | 6.02 (2.67) | 6.01 (1.86) | 5.69 (1.90) | 5.49 (1.53) |
| Platelets (10$^9$/L) | 207 (71) | 201 (77.5) | 191 (73) | 186 (82) | 210 (65) | 208 (70.8) |
| Neutrophils (10$^9$/L) | 3.01 (1.53) | 2.96 (1.34) | 3.23 (1.46) | 3.37 (1.29) | 2.93 (1.43) | 2.81 (1.29) |
| Lymphocyte (10$^9$/L) | 1.97 (0.85) | 1.84 (0.84) * | 1.91 (0.74) | 1.79 (0.89) | 2.03 (0.95) | 1.87 (0.80) |
| Monocyte (10$^9$/L) | 0.46 (0.18) | 0.5 (0.18) | 0.51 (0.25) | 0.53 (0.19) | 0.43 (0.17) | 0.48 (0.19) |
| HbA1c (%) | 7.36 (3.13) | 7.64 (3.61) | 8.15 (3.03) | 8.94 (3.66) | 6.87 (2.75) | 6.96 (2.64) |
| ALT (U/L) | 17.4 (10.9) | 15.55 (10.15) * | 19.4 (12.8) | 15.6 (12.8) | 16.3 (9.15) | 15.5 (8.8) |
| AST (U/L) | 16.9 (5.95) | 16.5 (5.88) | 16.9 (5.8) | 15.5 (7.1) | 16.9 (6) | 17.1 (4.75) |
| Creatinine (umol/L) | 64.5 (18) | 67 (25) | 72 (19) | 82 (30.5) * | 59 (14) | 61 (14.5) |
| Uric Acid (umol/L) | 308 (109.5) | 321.5 (113.75) | 330 (112) | 346 (162.5) | 302 (101.5) | 304 (118) |
| Total Cholesterol (mmol/L) | 4.47 ± 1.06 | 4.46 ± 0.92 | 4.35 ± 1.10 | 4.14 ± 0.85 | 4.47 ± 1.32 | 4.63 ± 0.91 |
| Triglyceride (mmol/L) | 1.37 (1.07) | 1.37 (0.87) | 1.31 (1.29) | 1.32 (0.88) | 1.37 (0.86) | 1.40 (0.90) |
| HDL-Cholesterol (mmol/L) | 1.2 (0.4) | 1.2 (0.49) | 1.10 (0.33) | 1.1 (0.35) | 1.27 (0.42) | 1.3 (0.5) |
| LDL-Cholesterol (mmol/L) | 2.5 (1.2) | 2.59 (1.03) | 2.35 (1.23) | 2.40 (1.09) | 2.60 (1.13) | 2.62 (1) |
| IL-6 (pg/ml) | 4.05 (4.28) | 4.19 (3.96) | 3.87 (4.75) | 4.43 (5.82) | 4.15 (3.93) | 4.16 (3.54) |
| IL-8 (pg/ml) | 50.7 (113.61) | 49.15 (99.49) | 49.05 (210.83) | 49 (185.73) | 46.3 (101.46) | 49.6 (79.8) |
| SAA (mg/L) | 8.59 (7.06) | 9.63 (9.06) | 8.49 (7) | 8.20 (6.78) | 8.69 (7.7) | 10.0 (8.71) |
| sIL-2R (U/mL) | 323 (155) | 349 (162.75) ** | 362 (157) | 421 (217) ** | 314 (149.75) | 329 (134.5) |

Data are presented as mean ± SD, median (IQR), or n (%). Abbreviations: BMI: body mass index; ASMI: appendicular skeletal muscle index; FCST: five chair stand test; HGS: hand grip strength; HbA1c: glycosylated hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SD: standard deviation; IQR: interquartile range. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for comparisons with no-sarcopenia.

BMI, AST, ALT, uric acid, HbA1c, IL-6, IL-8 and SAA; in the prevalence rate for type 2 diabetes and osteoporosis between sarcopenia and no-sarcopenia in men and women.

### 3.2. Associations of sIL-2R levels with sarcopenia, ASMI, HGS, gait speed and FCST

Significantly higher sIL-2R levels were found in sarcopenia group compared with no-sarcopenia group in all participants (421 (217) vs 362 (157) U/mL, $p < 0.001$; Table 1). This difference was still significant in men (Table 1, Fig. 1A), but not significant in women (Table 1, Fig. 2A). Meanwhile, male patients with low HGS, low gait speed or low FCST were more likely to have higher sIL-2R levels. And higher sIL-2R levels were just found in the low HGS group and the low gait speed group in female (Fig. S1).

Univariate correlation results were shown in Fig. 1B–E and Fig. 2B–E.
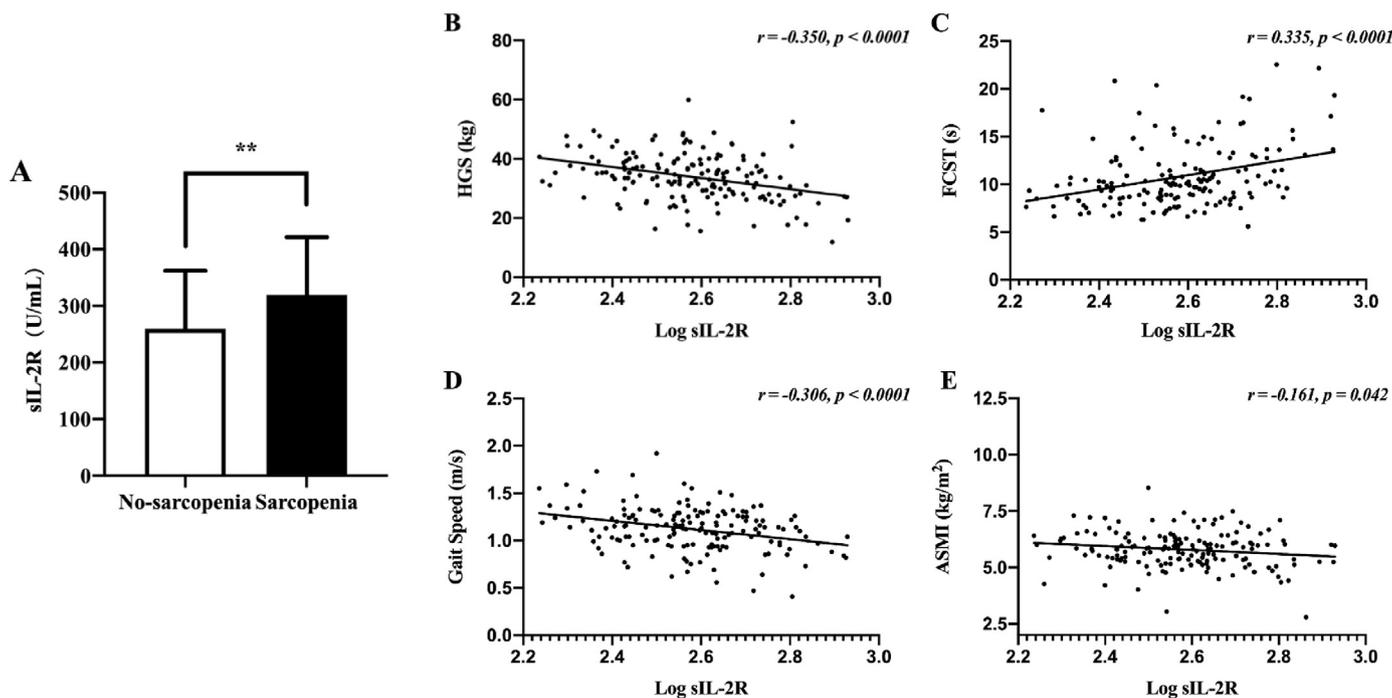


**Fig. 1.** (A) The sIL-2R level (median (IQR)) between sarcopenia and no-sarcopenia groups in male (n = 83, n = 77) (B–E) Simple correlation analysis of HGS, FCST, Gait Speed and ASMI with sIL-2R in male. Logarithm-transformed values of sIL-2R was used for analysis. **$p < 0.001$. sIL-2R: serum soluble IL-2 receptor; HGS: hand grip strength; FCST: five chair stand test; ASMI: appendicular skeletal muscle index; IQR: interquartile range.
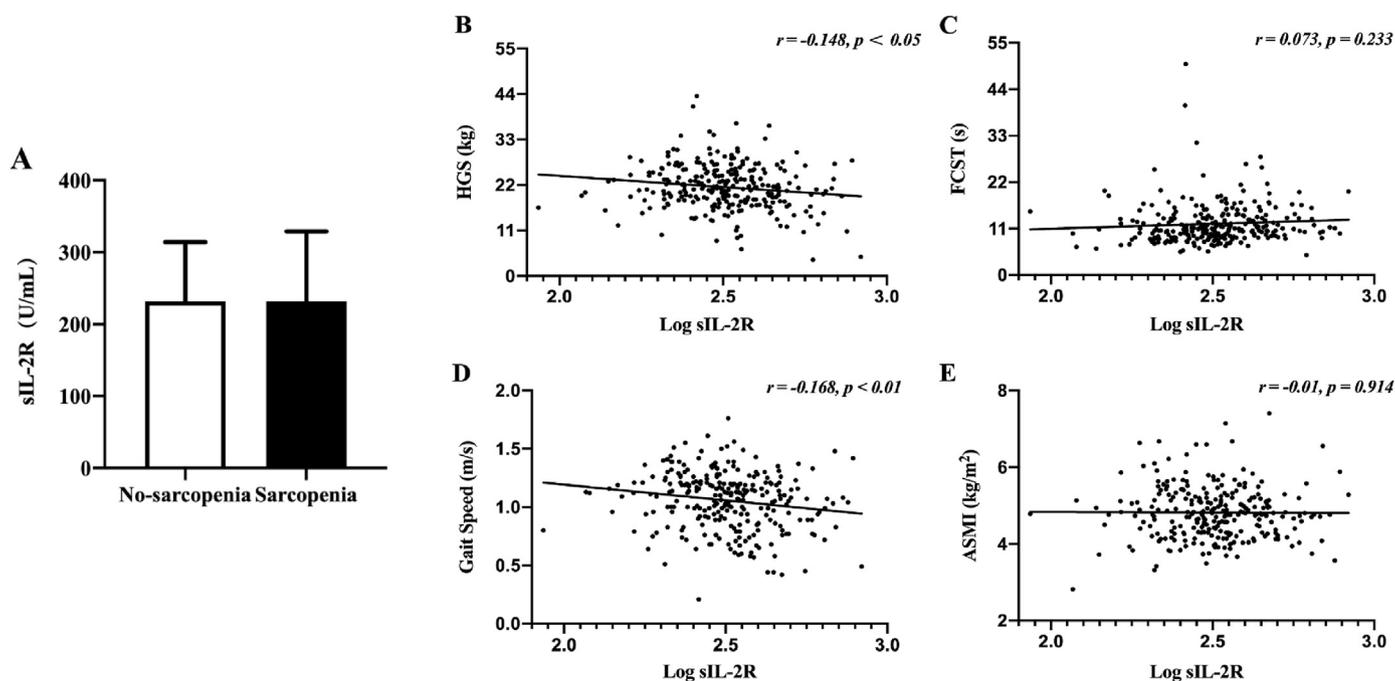
**Fig. 2.** (A) The sIL-2R level (median (IQR)) between sarcopenia and no-sarcopenia groups in female (n = 140, n = 129) (B–E) Simple correlation analysis of HGS, FCST, Gait Speed and ASMI with sIL-2R in female. Logarithm-transformed values of sIL-2R was used for analysis. sIL-2R: serum soluble IL-2 receptor; HGS: hand grip strength; FCST: five chair stand test; ASMI: appendicular skeletal muscle index; IQR: interquartile range.

In male, sIL-2R (logarithm-transformed) levels were negatively associated with HGS (r = −0.35, $p < 0.0001$), gait speed (r = −0.306, $p < 0.0001$) and ASMI (r = −0.161, $p < 0.05$), and positively associated with FCST (r = 0.335, $p < 0.0001$). In female, sIL-2R (logarithm-transformed) levels showed a significantly negative correlation with HGS (r = −0.148, $p < 0.05$) and gait speed (r = −0.168, $p < 0.01$).

### 3.3. sIL-2R is a risk factor for sarcopenia, low hand grip strength and low gait speed

We performed binary logistic regression analysis to determine the effect of sIL-2R on the risk of sarcopenia, low HGS, low gait speed, low FCST, and low ASMI (Table 2, Table 3, Table S2). In the univariate logistic analyses, the highest sIL-2R tertile was significantly associated with the risk of sarcopenia only in men (OR 3.306, 95%CI 1.496–7.302) compared with the lowest tertile. Meanwhile, we found the highest sIL-

2R tertile was associated with the risk of low HGS only in men, the risk of low gait speed in both sexes, and the risk of low FCST in both sexes in an unadjusted model. After fully adjusted in Model 3 (adjusting for age, BMI, MET, nutrition, alcohol, smoking, type 2 diabetes, osteoporosis, and coronary heart disease), the highest sIL-2R tertile was still an independent risk factor for sarcopenia (OR 2.892, 95%CI 1.207–6.935), low HGS (OR 4.322, 95%CI 1.342–13.922), and low gait speed (OR 3.124, 95%CI 1.071–9.110) only in men compared with the lowest tertile.

### 3.4. Diagnostic value of serum sIL-2R for sarcopenia and low HGS in male

All covariates in Model 3 were analyzed in a multivariate binary logistic regression analysis with backward selection, resulting in the elimination of some covariates (Table S3). The optimal model for sarcopenia (Nagelkerke $R^2$ = 0.266) in male included age, BMI, ever-drinker, type 2 diabetes, coronary heart disease and sIL-2R,

**Table 2**
ORs and 95%CI of sarcopenia by tertiles of sIL-2R concentrations.

| | | Odds ratio (95% confidence interval) | | | |
|---|---|---|---|---|---|
| | | Univariate | Model 1 | Model 2 | Model 3 |
| Male sarcopenia (n, %) | sIL-2R tertiles | | | | |
| 18, 23.4 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 25, 32.5 | Tertile 2 | 1.736 (0.793, 3.801) | 1.611 (0.711, 3.65) | 1.539 (0.674, 3.518) | 1.733 (0.730, 4.113) |
| 34, 63.0 | Tertile 3 | 3.306 (1.496, 7.302) | 2.774 (1.202, 6.403) | 2.684 (1.155, 6.236) | 2.892 (1.207, 6.935) |
| | p for trend | 0.003** | 0.017* | 0.022* | 0.017* |
| Female sarcopenia (n, %) | sIL-2R tertiles | | | | |
| 35, 27.1 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 47, 36.4 | Tertile 2 | 1.686 (0.932, 3.052) | 1.377 (0.741, 2.562) | 1.367 (0.732, 2.551) | 1.395 (0.744, 2.616) |
| 47, 36.4 | Tertile 3 | 1.686 (0.932, 3.052) | 1.287 (0.681, 2.432) | 1.316 (0.691, 2.506) | 1.424 (0.74, 2.738) |
| | p for trend | 0.086 | 0.433 | 0.398 | 0.281 |

Univariate: univariate logistic regression analyses for the association between sIL-2R tertiles and sarcopenia in female and male participants. Multivariate: multivariate logistic regression analyses to test whether sIL-2R tertiles are independently associated with sarcopenia in female and male participants. Model 1: Adjusted for age, BMI. Model 2: Adjusted for Model 1 + MET, nutrition. Model 3: Adjusted for Model 2 + alcohol, smoking, type 2 diabetes, osteoporosis, and coronary heart disease. Abbreviations: OR: odds ratio; 95% CI: 95% confidential interval. Dependent variable: sarcopenia; Independent variables: sIL-2R tertiles, age, BMI, MET, nutrition, smoking, alcohol, type 2 diabetes, osteoporosis, and coronary heart disease. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

**Table 3**
ORs and 95%CI of low HGS, low Gait speed, Low FCST and Low ASMI by tertiles of sIL-2R concentrations in male.

| | | Odds ratio (95% confidence interval) | | | |
|---|---|---|---|---|---|
| | | Univariate | Model 1 | Model 2 | Model 3 |
| Low HGS (n, %) | sIL-2R tertiles | | | | |
| 6, 16.2 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 11, 29.7 | Tertile 2 | 2.052 (0.698, 6.031) | 1.987 (0.651, 6.062) | 1.88 (0.570, 6.203) | 1.89 (0.558, 6.408) |
| 20, 54.1 | Tertile 3 | 4.608 (1.673, 12.695) | 4.075 (1.400, 11.860) | 4.227 (1.347, 13.265) | 4.322 (1.342, 13.922) |
| | *p* for trend | 0.002** | 0.008** | 0.011* | 0.012* |
| Low Gait Speed (n, %) | sIL-2R tertiles | | | | |
| 7, 15.9 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 18, 40.9 | Tertile 2 | 3.38 (1.272, 8.982) | 3.361 (1.222, 9.24) | 3.223 (1.168, 8.893) | 3.947 (1.331, 11.704) |
| 19, 43.2 | Tertile 3 | 3.567 (1.350, 9.427) | 2.905 (1.054, 8.008) | 2.796 (1.011, 7.733) | 3.124 (1.071, 9.110) |
| | *p* for trend | 0.012* | 0.051 | 0.063 | 0.056 |
| Low FCST (n, %) | sIL-2R tertiles | | | | |
| 11, 26.2 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 9, 21.4 | Tertile 2 | 0.781 (0.294, 2.075) | 0.693 (0.253, 1.899) | 0.655 (0.234, 1.830) | 0.657 (0.231, 1.863) |
| 22, 52.4 | Tertile 3 | 2.625 (1.114, 6.188) | 2.13 (0.865, 5.243) | 2.08 (0.828, 5.226) | 2.1 (0.829, 5.319) |
| | *p* for trend | 0.02* | 0.077 | 0.087 | 0.086 |
| Low ASMI (n, %) | sIL-2R tertiles | | | | |
| 45, 31.3 | Tertile 1 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 49, 34.0 | Tertile 2 | 2.178 (0.614, 7.729) | 1.995 (0.477, 8.352) | 1.671 (0.392, 7.126) | 2.686 (0.509, 14.178) |
| 50, 34.7 | Tertile 3 | 2.222 (0.627, 7.881) | 2.225 (0.526, 9.411) | 1.954 (0.455, 8.392) | 2.651 (0.579, 12.131) |
| | *p* for trend | 0.192 | 0.257 | 0.349 | 0.196 |

Univariate: univariate logistic regression analyses for the association between sIL-2R tertiles and low HGS, Gait Speed, FCST and ASMI. Multivariate: multivariate logistic regression analyses to test whether sIL-2R tertiles are independently associated with HGS, Gait Speed, FCST and ASMI. Model 1: Adjusted for age, BMI. Model 2: Adjusted for Model 1 + MET, nutrition. Model 3: Adjusted for Model 2 + alcohol, smoking, type 2 diabetes, osteoporosis, and coronary heart disease. Abbreviations: ASMI: appendicular skeletal muscle index; HGS: hand grip strength; FCST: five chair stand test; BMI: body mass index; MET: metabolic equivalent; OR: odds ratio; 95% CI: 95% confidential interval. Dependent variable: low HGS, Gait Speed, FCST and ASMI; Independent variables: sIL-2R tertiles, age, BMI, MET, nutrition, smoking, alcohol, type 2 diabetes, osteoporosis, and coronary heart disease. $*p < 0.05$, $**p < 0.01$.

corresponding to the equation for sarcopenia: logit (P1) = - 6.205 + 0.079 × age (years) - 0.083 × BMI (kg/m$^2$) - 0.393 × ever-drinker (yes = 1, no = 0) + 1.121 × type 2 diabetes (yes = 1, no = 0) + 0.995 × coronary heart disease (yes = 1, no = 0) + 0. L004 × sIL-2R (U/mL). The optimal model for low HGS (Nagelkerke R$^2$ = 0.391) in male included age, BMI, ever-smoker, ever-drinker, nutrition, type 2 diabetes and sIL-2R, corresponding to equation for low HGS: logit (P2) = - 7.196 + 0.057 × age (years) - 0.165 × BMI (kg/m$^2$) - 0.258 × ever-smoker (yes = 1, no = 0) - 0.572 × ever-drinker (yes = 1, no = 0) + 1.526 × nutrition (normal = 1, mild = 2, mid = 3, severe = 4) + 2.201 × type 2 diabetes (yes = 1, no = 0) + 0.005 × sIL-2R (U/mL). According to ROC curve analysis for diagnosing sarcopenia in men, Area Under the Curve (AUC) of logit (P1) was 0.752 (95% CI 0.677–0.827) of sIL-2R was 0.643 (95% CI 0.558–0.729). The optimal cutoff values of logit (P1) and sIL-2R were 0.53 and 519.5 U/mL, respectively. According to ROC curve analysis for low HGS in men, AUC of logit (P2) was 0.846 (95% CI 0.778, 0.914) of sIL-2R was 0.694 (95% CI 0.591–0.797). The optimal cutoff values of logit (P2) and sIL-2R were 0.205 and 538 U/mL, respectively (Fig. 3).

## 4. Discussion

In this study, we first found that the highest tertile of serum sIL-2R levels was independently associated with the risks of sarcopenia, low HGS, and low gait speed after fully adjusting for confounding factors only in men. No independent association between serum sIL-2R and muscle mass was observed in both men and women. Then, we established the optimal diagnostic models for sarcopenia and low HGS in men with better diagnostic accuracy and AUCs of 0.752 and 0.846, respectively.

sIL-2R is a soluble form of IL-2 receptor found in the circulation of healthy individuals. Generally, it was considered a negative feedback factor to keep immune activation in check [21,22]. When an individual develops infections, inflammation or autoimmune diseases, more IL-2 receptors will be sloughed off from the T lymphocytes membrane [21] to regulate immune response, accompanied by a further sIL-2R increase [11,13]. Clinical and animal studies have confirmed that sIL-2R was elevated in inflammatory diseases, such as rheumatoid hepatitis, coronary artery disease and arthritis [11]. In addition, a previous study also
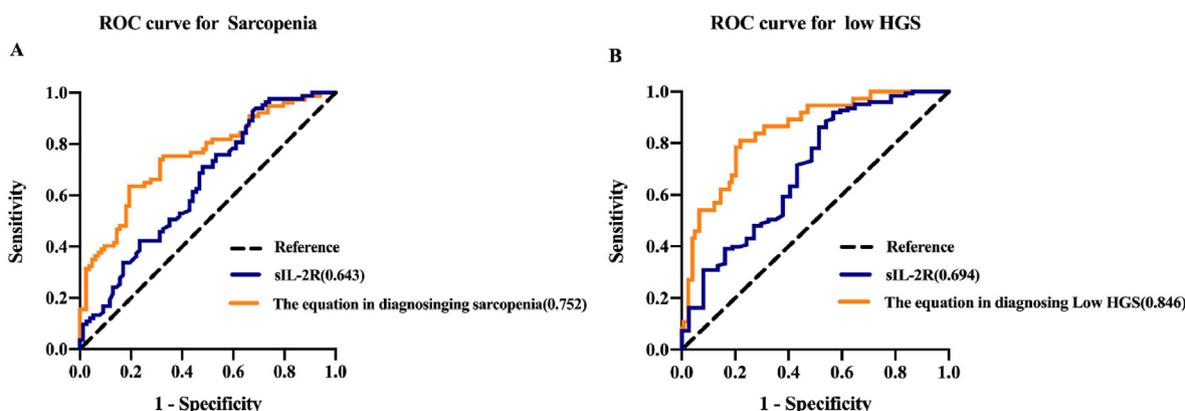


**Fig. 3.** ROC curves of sIL-2R and the equation in diagnosing (A) sarcopenia and (B) low HGS in man (n = 77, n = 37). Reference is the tracing of ROC analysis of equation in diagnosing sarcopenia and low HGS. Abbreviations: ROC: Receiver Operating Characteristic; HGS: hand grip strength; sIL-2R: serum soluble IL-2 receptor.

showed a higher level of serum sIL-2R was associated with the risk of progression and relapse for multiple sclerosis characterized by weakness of the limbs [8,23]. Similar to the above studies, our data of male patients identified an increasing level of serum sIL-2R in sarcopenia, a chronic inflammatory disease associated with age.

Furthermore, our results in male suggested that sIL-2R could be an independent risk factor for sarcopenia, in which inflammation and satellite cell function may be involved [24–26]. Inflammation had been proved to potentiate catabolism of muscle proteins [16,17], which was able to be suppressed by IL-2/IL-2R reaction. Previous studies showed that recombinant IL-2, such as L19-IL2 (a fusion antibody specific to extra-domain B of fibronectin containing an active human IL-2 molecule) and IL-2/anti-IL-2 mAb (a complex composed of IL-2 and anti-IL-2 monoclonal antibody) could activate IL-2R to attenuate inflammation response [27,28]. Nevertheless, sIL-2R can competitively bind to IL-2 with IL-2R to suppress the anti-inflammation function, resulting in muscle loss [12,13]. In addition, T cells activated by IL-2/IL-2R reaction have been found to be involved in the repair of muscle injuries by the expansion of satellite cells [15,29]. Treg cell, a kind of immunosuppressive T lymphocyte, was also reported to be activated by IL-2/IL-2R reaction to promote muscle growth and injury repair through promoting satellite cells proliferation and migration [13,14,30–33]. A high level of sIL-2R could function as a sink for IL-2, leading to the attenuation of T cell activation and the potentiation of muscle atrophy. In our study, the male had higher sIL-2R levels than females in both sarcopenia and no-sarcopenia group, contradicting the conventional notion that sIL-2R has no gender differences in adults [34]. It may be explained by a decreased number of Tregs cells contributing to the majority of sIL-2R levels, which is related to sex hormones concentrations change in women after menopause [35,36]. We also found that the highest tertile of sIL-2R was independently associated with the risk of sarcopenia compared to the lowest tertile only in men after adjusting for age, BMI, MET, nutrition, alcohol, smoking, type 2 diabetes, osteoporosis, and coronary heart disease (Model 3) (Table 2). Further analysis showed that the highest tertile of sIL-2R had an independent association with the risk of low HGS and the risk of low gait speed only in men. However, no significant association was found between sIL-2R tertiles and low muscle mass in either men or women (Table 3). This suggested that the occurrence of sarcopenia was more susceptible to sIL-2R in men than in women, and that the effects of sIL-2R on sarcopenia mainly focused on muscle strength and physical performance, rather than muscle mass. This was of great significance for clinical practice in view of the higher predictive value of muscle strength for predicting age-related functional loss and adverse health outcomes than muscle mass [37]. Using a combination of sIL-2R (AUCs for diagnosing sarcopenia and low HGS in men were 0.643 and 0.694) and other indicators, we further developed the models for evaluating the risks of sarcopenia and low grip strength, respectively, in men, in order to increase diagnostic accuracy. Their AUCs were 0.752 and 0.846 (Fig. 3), showing higher diagnostic values compared with the models for sarcopenia and low HGS in previous studies [38–40], and the cutoff values were 0.53 and 0.205, correspondingly.

There are still some limitations to our study. First, it is a cross-sectional study of failure to reflect the causality, thereby further longitudinal studies are needed. Second, our study is a single-center analysis that lacks universality, requiring multicenter work to confirm our conclusion. Third, this is a non-validating study, requiring internal and external validation to make our models more convincing in predicting low HGS and sarcopenia. Forth, we don't include a population without high fracture risk for comparison, and additional research is required to broaden our perspective.

Nevertheless, our study also has notable strengths. First, physical performance was evaluated through both 6-m gait speed test and FCST, allowing for a more accurate diagnosis of sarcopenia, while most studies have included one of the two. Second, to our knowledge, this is the first study to illustrate the relationship between sIL-2R and sarcopenia in

clinical. Third, we provided new approaches for diagnosing sarcopenia and low HGS in men. In addition, our study was performed in the population at high risk of osteoporotic fracture and was of certain clinical application value.

In conclusion, this study first found that, in population at high risk of osteoporotic fracture, sarcopenia individuals have a higher level of serum sIL-2R than no-sarcopenia. sIL-2R is an independent risk factor for sarcopenia and low HGS only in men. Our equation has high diagnostic values for sarcopenia and low HGS in older men at high risk of fractures. More longitudinal studies are required to figure out the causal link between sIL-2R and sarcopenia, therefore these findings should be regarded with caution.

## Authors' contributions

Hui Sheng generated the idea and led the present study. Jiaying Ge and Jiangping Zeng contributed equally to conducting all analyses, interpreting the results and drafting the manuscript. Nannan Li, Huihui Ma, Zheng Zhao, Siqi Sun and Yujie Jing were responsible for data collection. Ran Cui, Chunhua Qian, Zhaoliang Fei and Shen Qu oversaw the data collection and guided analyses.

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## Declarations

Ethics approval The study was conducted in accordance with the Declaration of Helsink and approved by the Shanghai Tenth People's Hospital Ethics Committee (protocol code 22K29 and date of approval: 24 January 2022).

## Consent to participate

The requirement for informed consent was waived due to the retrospective design of the study.

## Consent for publication

All authors read and approved the final manuscript for publication.

## Data availability statement

The data presented in the study are available within the article.

## Declaration of competing interest

Jiaying Ge, Jiangping Zeng, Nannan Li, Huihui Ma, Zheng Zhao, Siqi Sun, Yujie Jing, Chunhua Qian, Zhaoliang Fei, Shen Qu, Ran Cui, and Hui Sheng declare that they have no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2022.10.017.

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