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Original Article

Sarcopenia severity and its prognostic value for structural and functional progression in elderly patients with knee osteoarthritis: a 24-month retrospective cohort study

Tao Wen*, Jiazhong Ji*, Yihui Tu

Joint Surgery Department, Yangpu Hospital, School of Medicine, Tongji University, Shanghai 200090, China.
**Equal contributors.*

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Abstract: Background: Sarcopenia is a age-related symptom characterized by loss of muscle mass and strength, which often coexists with knee osteoarthritis (KOA). Objective: In the current study, the association between sarcopenia severity and the progression of KOA among elderly patients was explored. Methods: A total of 226 KOA patients aged ≥ 60 years were followed for 24 months. Sarcopenia was diagnosed into non-sarcopenia, probable, confirmed, and severe categories. Outcomes included Kellgren-Lawrence (KL) progression, joint-space width (JSW) narrowing, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) deterioration, functional decline, and biochemical changes. Multivariate logistic regression identified independent predictors. Model performance was evaluated using ROC curves, calibration plots, and decision-curve analysis (DCA). Results: Radiographic progression increased stepwise with sarcopenia severity (KL progression: 25% to 65%; JSW narrowing: 30% to 68%, $P < 0.001$). Confirmed or severe sarcopenia independently predicted 24-month progression (OR = 2.58, 95% CI 1.33-5.01). Additional predictors included slower gait speed, lower phase angle, elevated CRP and IL-6, reduced albumin, and lower 25 (OH)D levels. The multivariable model integrating these factors achieved strong discrimination (AUC = 0.86), excellent calibration, and meaningful net clinical benefit on DCA, outperforming sarcopenia severity alone (AUC = 0.68). Kaplan-Meier curves demonstrated earlier progression in more severe sarcopenia groups. Conclusions: Sarcopenia severity is strongly associated with earlier KOA progression by interacting with biomechanical, inflammatory, and nutritional pathways. Thus, a multidimensional model incorporating functional, inflammatory, and nutritional parameters substantially improves prognostic accuracy.

Keywords: Sarcopenia, knee osteoarthritis, muscle weakness, aging, prognosis

Introduction

As a highly prevalent degenerative joint disease, knee osteoarthritis (KOA) constitutes a major cause of pain, disability, and reduced quality of life in the aging population. Epidemiological studies indicate that the prevalence of KOA increases with age, obesity, weight-bearing joint involvement, and metabolic factors, etc. [1, 2]. With the aging of the global population, KOA is now placing a great burden on the public health system and caregivers, prompting the need for identifying the prognostic factors of disease progression.

Among multiple factors influencing the progression of KOA, sarcopenia has emerged as a major geriatric syndrome associated with falls, disability, and reduced autonomy [3]. The disease is defined as the age-related progressive loss of skeletal muscle mass, strength, and physical performance, the pathophysiology of which includes neuromuscular degeneration, mitochondrial dysfunction, increased inflammatory signaling, and diminished anabolic responses in older skeletal muscle [3, 4]. In clinical practice, sarcopenia is diagnosed by metrics of muscle mass, muscle strength, and physical performance [5]. The coexistence of KOA and sarcopenia is biologically plausible and is drawing growing interest from clinicians. Both conditions share several mechanistic pathways, including chronic low-grade inflammation, oxidative stress, alterations in

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muscle-bone interplay, and reduced physical activity due to pain and joint dysfunction, which may interact to accelerate musculoskeletal decline [6, 7]. For example, muscle weakness typical of sarcopenia may reduce dynamic joint stability, leading to altered load distribution across the knee joint, increased cartilage stress, subchondral bone changes, and ultimately accelerate KOA progression [8, 9]. Conversely, KOA pain and mobility limitations may reduce muscle use, induce muscle atrophy, and thus potentiate sarcopenia, which suggests a potential bidirectional relationship between the two disorders [10].

From a prognostic perspective, while many studies have investigated risk factors for incident KOA, less is known about predictors of disease progression - that is, the rate of worsening structural damage and/or functional decline. Established prognostic factors for KOA progression include baseline radiographic severity, malalignment, varus deformities, obesity, and inflammatory biomarkers. However, the evidence for muscle factors in predicting progression has been inconsistent [11, 12]. For instance, recent longitudinal data have found that thigh muscle strength decline preceded symptomatic KOA development in some cohorts [13]. Another study reported that reduced quadriceps cross-sectional area and increased intramuscular fat predicted KOA progression on MRI [14].

Specifically, the role of sarcopenia as a prognostic indicator of faster progression in elderly KOA patients has been less systematically examined. A recent study found that baseline sarcopenia (defined by muscle mass and strength) was associated with a greater risk of symptomatic KOA over four years (OR ≈ 2.3) but did not show a clear link with radiographic progression in that sample [10]. A more recent study in an older Chinese population reported that baseline sarcopenia (per AWGS 2019) was associated with incident symptomatic KOA, particularly in women, but the relationship with structural progression and progression velocity remains underexplored [15]. Additional cross-sectional evidence links lower muscle mass index with prevalent KOA and worse functional status [16].

Mechanistically, muscle weakness or atrophy may contribute to KOA progression via multiple pathways: (1) decreased periarticular muscle support results in higher joint loading and shear forces; (2) reduced muscle-derived myokines and altered muscle-bone crosstalk that may impair cartilage homeostasis; (3) sarcopenia is often accompanied by increased fat infiltration (myosteatosis), systemic inflammation, and insulin resistance, which may exacerbate cartilage catabolism and subchondral bone changes; and (4) sarcopenic individuals may have diminished capacity for joint-protective movement patterns and reduced rehabilitation responses. These mechanistic links make sarcopenia a plausible modifiable risk factor for more rapid KOA progression, particularly in older patients whose muscle reserve is already compromised.

Given the high prevalence of both sarcopenia and KOA in the elderly, and the limited effective disease-modifying therapies for KOA, identifying prognostic markers of rapid progression is clinically important. If sarcopenia is shown to predict accelerated structural or symptomatic deterioration in KOA, it would support early screening and targeted interventions aimed at preserving muscle mass and function as a means to slow KOA progression. Therefore, in a cohort of elderly patients (≥ 60 years) with established knee osteoarthritis (Kellgren-Lawrence grade II-III), the present study aims to investigate whether the presence of sarcopenia is independently associated with a faster rate of disease progression. We also attempt to explore potential mediating factors and whether the prognostic association is modified by sex, baseline obesity status, or baseline radiographic severity. By focusing on progression rate rather than merely incidence, and by integrating muscle mass/strength assessment into the prognostic paradigm of KOA in the older population, this study may provide data to support the integration of sarcopenia screening into KOA management and prognostication.

Methods

Case selection and inclusion criteria

A retrospective cohort study was conducted in elderly patients (≥ 60 years) diagnosed with KOA and admitted to the Rheumatology and Orthopedic Departments of Yangpu Hospital, Tongji University, between January 2020 and

December 2024. KOA was radiographically confirmed based on the Kellgren-Lawrence (KL) grading system. Patients were eligible for inclusion if: 1) they were within KL grade II-III; 2) were aged 60 years or older; 3) showed reduced physical activity and decreased grip strength during clinical screening; 4) had completed all required assessments; and 5) had complete clinical records available for analysis. Patients were excluded if: 1) had secondary knee osteoarthritis; 2) had long-term bedridden status that prevented valid physical performance testing; 3) a history of knee joint surgery, or inflammatory joint diseases such as rheumatoid arthritis; 4) were experiencing active inflammatory or infectious conditions; 5) had advanced malignancy, severe cardiovascular dysfunction, or recent cerebrovascular events; or 6) any key clinical, functional, or radiographic data were missing or incomplete. All participants underwent standardized baseline and 24-month evaluations. This retrospective study was approved by the Ethics Committee of Yangpu Hospital, and the requirement for informed consent was waived due to the use of de-identified data.

Data collection and variable definitions

Diagnosis and staging of sarcopenia: Sarcopenia was diagnosed according to the Asian Working Group for Sarcopenia 2019 (AWGS 2019) criteria based on the measurements of muscle mass, strength, and physical performance. Appendicular skeletal-muscle mass (ASM) was quantified by dual-energy X-ray absorptiometry or bioelectrical-impedance analysis and normalized for height^2 (ASM/height^2): thresholds for low muscle mass were < 7.0 kg/m^2 for men and < 5.4 kg/m^2 for women. Muscle strength was measured using a Jamar handgrip dynamometer (< 28 kg for men, < 18 kg for women). Physical performance was evaluated using the Short Physical Performance Battery (SPPB ≤ 9) and the Timed Up-and-Go test (> 12 s). Patients were classified into four categories - non-sarcopenia, probable, confirmed, and severe - reflecting increasing neuromuscular impairment.

Assessment of KOA progression: Radiographic, clinical, and biochemical parameters were collected at baseline and after 24 months from patient records. Radiographic progression was defined as an increase of ≥ 1 KL grade or ≥ 0.5 mm reduction in medial joint-space width (JSW) on standardized standing anteroposterior knee radiographs. Pain, stiffness, and physical function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Functional capacity was quantified by gait speed, grip strength, and bioimpedance-derived phase angle. Laboratory analyses measured inflammatory and metabolic biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), matrix metalloproteinase-3 (MMP-3), malondialdehyde (MDA), superoxide dismutase (SOD), albumin, prealbumin, and 25-hydroxyvitamin D [25(OH)D], representing inflammation, oxidative stress, and nutritional status, respectively.

Subgroup and predictive-model analyses: Sex-specific and alignment-specific subgroup analyses were performed to examine effect modification. Lower-limb alignment was determined from long-leg radiographs, with varus malalignment > 5° as pathologic. Multivariate logistic regression identified independent predictors of 24-month radiographic progression from candidate demographic, biomechanical, inflammatory, and nutritional variables. Model performance was assessed for discrimination, calibration, and clinical utility through receiver-operating-characteristic (ROC) analysis, the Hosmer-Lemeshow test, and decision-curve analysis (DCA).

Statistical analysis

All analyses were performed using SPSS v25.0 (IBM, USA) and R v4.3.1 (R Foundation, Austria). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and compared using one-way ANOVA or Kruskal-Wallis tests with post-hoc Bonferroni correction. Categorical variables were compared using χ^2 or Fisher's exact tests. Linear-trend analysis across sarcopenia categories employed polynomial contrasts. Univariate logistic regression identified potential predictors of radiographic progression ($P < 0.10$), which were entered into multivariate regression using backward stepwise likelihood-ratio selection. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Model discrimination was quantified by the area under the ROC curve (AUC), and calibration analy-

Table 1. Baseline demographic, clinical, and biochemical characteristics across sarcopenia categories (AWGS 2019)

Variable	Non-sarcopenia (n = 82)	Probable (n = 61)	Confirmed (n = 47)	Severe (n = 36)	*p* value
Age (years)	68.5 ± 6.1	70.3 ± 6.4	71.7 ± 6.6	73.4 ± 6.8	< 0.001
Female sex (%)	60.97	63.93	65.95	66.66	0.643
BMI (kg/m^2)	25.30 ± 3.60	24.20 ± 3.40	23.40 ± 3.20	22.70 ± 3.10	< 0.001
Hypertension (%)	46.34	47.54	48.94	52.77	0.731
Diabetes (%)	18.29	21.31	23.40	25.00	0.612
ASM index (kg/m^2)	7.41 ± 0.73	6.93 ± 0.68	6.22 ± 0.61	5.65 ± 0.59	< 0.001
Handgrip strength (kg)	27.60 ± 5.80	23.90 ± 5.60	20.50 ± 5.10	17.20 ± 4.70	< 0.001
Gait speed (m/s)	1.08 ± 0.18	0.94 ± 0.17	0.82 ± 0.15	0.68 ± 0.14	< 0.001
Phase angle (°)	6.12 ± 0.65	5.71 ± 0.68	5.22 ± 0.71	4.78 ± 0.69	< 0.001
WOMAC Pain (0-20)	7.80 ± 3.90	8.20 ± 4.00	8.70 ± 4.20	9.00 ± 4.30	0.363
WOMAC Function (0-68)	25.40 ± 10.20	27.10 ± 10.80	29.80 ± 11.20	32.10 ± 11.60	0.076
CRP (mg/L)	2.40 ± 1.60	3.60 ± 1.90	4.90 ± 2.20	6.20 ± 2.70	< 0.001
IL-6 (pg/mL)	3.80 ± 1.40	5.10 ± 1.90	6.70 ± 2.40	8.30 ± 2.90	< 0.001
TNF-α (pg/mL)	5.50 ± 2.10	6.90 ± 2.40	8.10 ± 2.80	9.50 ± 3.00	< 0.001
MMP-3 (ng/mL)	52.30 ± 17.80	63.60 ± 20.50	74.80 ± 24.10	85.20 ± 25.60	< 0.001
MDA (nmol/mL)	3.10 ± 0.90	3.80 ± 1.00	4.60 ± 1.10	5.30 ± 1.20	< 0.001
SOD (U/mL)	116.80 ± 20.40	104.50 ± 18.90	92.30 ± 16.80	83.60 ± 15.50	< 0.001
Albumin (g/L)	42.80 ± 3.80	41.20 ± 3.60	39.60 ± 3.50	38.10 ± 3.20	< 0.001
Prealbumin (mg/L)	242.60 ± 36.50	227.40 ± 35.80	211.30 ± 33.40	196.70 ± 32.90	< 0.001
25(OH)D (ng/mL)	27.10 ± 7.30	23.80 ± 7.00	20.90 ± 6.60	17.80 ± 6.00	< 0.001

Abbreviations: AWGS = Asian Working Group for Sarcopenia; ASM = appendicular skeletal-muscle mass; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; MMP-3 = matrix metalloproteinase-3; MDA = malondialdehyde; SOD = superoxide dismutase; 25(OH)D = 25-hydroxyvitamin D; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

sis was performed using the Hosmer-Lemeshow goodness-of-fit test. All statistical tests were two-sided, with $P < 0.05$ considered as statistically significant.

Results

Baseline characteristics

The current analysis enrolled 226 elderly KOA patients, of which 82 were classified as non-sarcopenia, 61 as probable, 47 as confirmed, and 36 as severe sarcopenia. As shown in **Table 1**, higher sarcopenia severity was associated with older age, lower BMI, and progressively reduced muscle mass, handgrip strength, gait speed, and phase angle. Each higher sarcopenia category exhibited significantly poorer muscle quantity and quality than the preceding category. Inflammatory and oxidative-stress biomarkers increased in a graded fashion from non-sarcopenia to severe sarcopenia, whereas antioxidant and nutritional markers showed the opposite pattern. These differences collectively reflected a clear severity-dependent deterioration in musculoskeletal, inflammatory, and metabolic status in KOA patients.

Longitudinal changes over 24 months

Across all the four groups, WOMAC pain, function, and total scores worsened over 24 months, but the magnitude of deterioration increased stepwise with sarcopenia severity (**Table 2**). Patients with confirmed or severe sarcopenia showed the greatest functional decline and the largest reductions in gait speed, handgrip strength, and appendicular skeletal-muscle mass. A similar gradient was observed for biochemical markers, including CRP, IL-6, TNF-α, MMP-3, and MDA, which rose more sharply in the severe group. However, antioxidant and nutritional markers declined to a greater extent. These findings demonstrated that sarcopenia severity is strongly associ-

Table 2. Radiographic, functional, anthropometric, and biochemical outcomes and 24-month changes across sarcopenia categories (AWGS 2019)

Parameter	Non-sarcopenia (n = 82)	Probable (n = 61)	Confirmed (n = 47)	Severe (n = 36)	*p* value
Clinical Function (WOMAC)					
WOMAC pain (0-20, 24 mo)	9.70 ± 4.20	10.80 ± 4.40	11.70 ± 4.60	12.90 ± 4.80	< 0.001
Δ pain (points)	+1.90 ± 1.70	+2.60 ± 1.80	+3.00 ± 2.00	+3.90 ± 2.10	< 0.001
WOMAC function (0-68, 24 mo)	31.90 ± 11.40	35.60 ± 11.80	39.60 ± 12.40	43.80 ± 12.90	< 0.001
Δ function (points)	+6.50 ± 5.30	+8.50 ± 5.70	+9.80 ± 6.00	+11.70 ± 6.40	< 0.001
WOMAC total (24 mo)	50.90 ± 12.30	57.80 ± 13.00	63.50 ± 13.40	69.10 ± 13.90	< 0.001
Δ WOMAC total	+8.60 ± 7.10	+11.10 ± 7.40	+12.70 ± 7.80	+14.90 ± 8.10	< 0.001
Anthropometric and Muscle Parameters					
BMI (kg/m^2, 24 mo)	25.00 ± 3.40	24.10 ± 3.20	23.10 ± 3.10	22.30 ± 3.00	< 0.001
Δ BMI (kg/m^2)	-0.30 ± 0.50	-0.50 ± 0.60	-0.70 ± 0.70	-0.90 ± 0.80	< 0.001
Weight change (%)	-1.10 ± 2.40	-2.10 ± 2.70	-3.00 ± 2.80	-3.70 ± 3.10	< 0.001
Gait speed (m/s, 24 mo)	1.02 ± 0.18	0.88 ± 0.18	0.76 ± 0.16	0.63 ± 0.14	< 0.001
Δ gait speed (m/s)	-0.05 ± 0.07	-0.07 ± 0.08	-0.08 ± 0.09	-0.09 ± 0.09	< 0.001
ASM/height^2 (kg/m^2, 24 mo)	7.21 ± 0.71	6.68 ± 0.64	5.92 ± 0.59	5.31 ± 0.57	< 0.001
Δ ASM/height^2 (kg/m^2)	-0.20 ± 0.24	-0.25 ± 0.26	-0.30 ± 0.27	-0.34 ± 0.29	0.018
Handgrip strength (kg, 24 mo)	26.90 ± 5.50	22.60 ± 5.30	19.30 ± 4.80	16.10 ± 4.50	< 0.001
Δ Handgrip (kg)	-0.70 ± 1.60	-1.30 ± 1.70	-1.20 ± 1.50	-1.10 ± 1.50	0.048
Inflammatory and Cartilage Markers					
CRP (mg/L, 24 mo)	3.20 ± 1.70	4.50 ± 2.10	6.10 ± 2.30	7.40 ± 2.60	< 0.001
Δ CRP (mg/L)	+0.80 ± 1.00	+0.90 ± 1.10	+1.20 ± 1.20	+1.30 ± 1.30	0.004
IL-6 (pg/mL, 24 mo)	4.40 ± 1.60	6.00 ± 2.10	7.80 ± 2.60	9.60 ± 3.00	< 0.001
Δ IL-6 (pg/mL)	+0.60 ± 0.80	+0.90 ± 0.90	+1.10 ± 1.00	+1.30 ± 1.10	0.001
TNF-α (pg/mL, 24 mo)	6.10 ± 2.20	7.40 ± 2.50	8.90 ± 2.90	10.30 ± 3.20	< 0.001
Δ TNF-α (pg/mL)	+0.60 ± 0.70	+0.50 ± 0.80	+0.80 ± 0.90	+0.80 ± 1.00	0.045
MMP-3 (ng/mL, 24 mo)	56.40 ± 18.10	68.20 ± 21.00	79.50 ± 23.70	91.40 ± 26.20	< 0.001
Δ MMP-3 (ng/mL)	+4.10 ± 5.50	+4.60 ± 5.90	+4.70 ± 6.20	+6.20 ± 6.40	0.011
Oxidative Stress and Nutritional Markers					
MDA (nmol/mL, 24 mo)	3.50 ± 0.90	4.30 ± 1.00	5.00 ± 1.10	5.90 ± 1.30	< 0.001
Δ MDA (nmol/mL)	+0.40 ± 0.50	+0.50 ± 0.60	+0.40 ± 0.50	+0.60 ± 0.60	0.032
SOD (U/mL, 24 mo)	113.10 ± 19.90	100.20 ± 18.30	87.50 ± 15.80	78.20 ± 14.90	< 0.001
Δ SOD (U/mL)	-3.70 ± 6.80	-4.30 ± 7.10	-4.80 ± 7.30	-5.40 ± 7.60	0.192
Albumin (g/L, 24 mo)	42.10 ± 3.70	40.40 ± 3.50	38.70 ± 3.40	37.20 ± 3.10	< 0.001
Δ Albumin (g/L)	-0.70 ± 1.00	-0.80 ± 1.10	-0.90 ± 1.20	-0.90 ± 1.20	0.041
Prealbumin (mg/L, 24 mo)	238.90 ± 36.20	223.80 ± 35.40	208.20 ± 33.00	193.60 ± 32.40	< 0.001
Δ Prealbumin (mg/L)	-3.70 ± 4.60	-3.60 ± 4.80	-3.10 ± 5.00	-3.10 ± 5.10	0.078
25(OH)D (ng/mL, 24 mo)	25.60 ± 7.00	21.80 ± 6.60	19.20 ± 6.20	15.90 ± 5.80	< 0.001
Δ 25(OH)D (ng/mL)	-1.50 ± 2.30	-2.00 ± 2.50	-1.70 ± 2.30	-1.90 ± 2.40	0.228
Total cholesterol (mmol/L, 24 mo)	4.49 ± 0.73	4.38 ± 0.70	4.24 ± 0.67	4.10 ± 0.64	0.046
Fasting glucose (mmol/L, 24 mo)	5.10 ± 0.74	5.24 ± 0.78	5.36 ± 0.81	5.48 ± 0.85	0.038

Abbreviations: AWGS = Asian Working Group for Sarcopenia; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; ASM = appendicular skeletal muscle mass; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; MMP-3 = matrix metalloproteinase-3; MDA = malondialdehyde; SOD = superoxide dismutase; 25(OH)D = 25-hydroxyvitamin D.

ated with faster functional and metabolic deterioration.

Radiographic progression

Radiographic outcomes also varied substantially among the four groups. As illustrated in **Table 3**, the proportion of patients with KL grade progression and joint-space-width narrowing increased progressively from the non-sarcopenia to the severe sarcopenia category. Severe sarcopenia was associated with more than double the rate of structural progression compared with non-sarcopenia. These severity-

Table 3. Comparison of radiographic progression among sarcopenia categories

Parameter	Non-sarcopenia (n = 82)	Probable (n = 61)	Confirmed (n = 47)	Severe (n = 36)	*p* value
Kellgren-Lawrence progression (%)	25	54	54	65	< 0.001
Joint space width progression (%)	30	45	58	68	< 0.001

Table 4. Univariate and multivariate predictors of 24-month KOA progression

Variable	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p* value
Age (per year)	1.06 (1.02-1.10)	0.003	1.04 (1.00-1.09)	0.038
Female sex	1.48 (0.91-2.38)	0.112	1.22 (0.73-2.06)	0.441
BMI (per kg/m^2)	0.94 (0.88-0.99)	0.041	0.95 (0.88-1.02)	0.182
Sarcopenia (confirmed/severe vs. non-)	2.92 (1.76-4.83)	< 0.001	2.58 (1.33-5.01)	0.005
Gait speed (per 0.1 m/s decrease)	1.55 (1.24-1.94)	< 0.001	1.87 (1.21-2.90)	0.004
Phase angle (per 0.5° decrease)	1.37 (1.13-1.67)	0.001	1.54 (1.13-2.09)	0.006
Weight loss > 5%	2.06 (1.14-3.72)	0.017	1.89 (1.02-3.49)	0.043
Physical activity < 2 h/week	1.84 (1.03-3.29)	0.039	1.68 (0.92-3.10)	0.089
CRP (per 1 mg/L increase)	1.25 (1.12-1.38)	< 0.001	1.26 (1.09-1.46)	0.002
IL-6 (per 1 pg/mL increase)	1.18 (1.07-1.29)	< 0.001	1.11 (1.02-1.21)	0.014
TNF-α (per 1 pg/mL increase)	1.09 (1.02-1.17)	0.011	1.06 (0.98-1.15)	0.137
MMP-3 (per 10 ng/mL increase)	1.22 (1.10-1.35)	< 0.001	1.15 (1.04-1.27)	0.007
MDA (per 1 nmol/mL increase)	1.28 (1.08-1.53)	0.004	1.22 (1.01-1.49)	0.038
SOD (per 10 U/mL increase)	0.77 (0.65-0.90)	0.001	0.83 (0.71-0.97)	0.019
Albumin (per 1 g/L increase)	0.92 (0.87-0.97)	0.003	0.93 (0.88-0.99)	0.026
Prealbumin (per 10 mg/L increase)	0.95 (0.91-0.99)	0.012	0.96 (0.92-1.01)	0.089
25(OH)D (per 5 ng/mL increase)	0.93 (0.89-0.97)	< 0.001	0.93 (0.89-0.98)	0.011
Baseline KL grade (per grade)	1.83 (1.18-2.84)	0.007	1.61 (1.03-2.52)	0.035
Baseline WOMAC total (per 10 points)	1.24 (1.03-1.48)	0.024	1.18 (0.97-1.44)	0.096

Abbreviations: OR = odds ratio; CI = confidence interval; KL = Kellgren-Lawrence; AWGS = Asian Working Group for Sarcopenia; BMI = body mass index; CRP = C-reactive protein.

dependent structural changes further support sarcopenia as a strong determinant of radiographic KOA progression.

Independent predictors of disease progression

The univariate analysis (**Table 4**) identified multiple predictors of radiographic progression, including sarcopenia severity, slower gait speed, lower phase angle, inflammatory activation, metabolic insufficiency, and higher baseline KL grade. After adjustment for covariates, confirmed or severe sarcopenia remained independently associated with progression, together with gait speed, phase angle, CRP, IL-6, albumin, and 25(OH)D. These findings indicated that sarcopenia-related neuromuscular impairment, systemic inflammation, and nutritional deficits jointly contribute to KOA progression risk.

Subgroup analyses

Sex-stratified and alignment-stratified results (**Table 5**) demonstrated notable effect modification. The association between sarcopenia and KOA progression was stronger in women than in men, and was particularly pronounced in individuals with varus malalignment. In these subgroups, lower muscle strength, slower gait speed, greater weight loss, and lower vitamin D levels all conferred significantly higher progression risk. In contrast, these associations were weaker or nonsignificant in men and individuals with neutral alignment. These findings suggested that biomechanical loading and sex-related

Table 5. Subgroup analysis stratified by sex and lower-limb alignment

Variable	Male (n = 93)	Female (n = 155)	Neutral alignment (≤ 5°, n = 142)	Varus alignment (> 5°, n = 106)
Sarcopenia (yes vs. no)	OR = 1.89 (95% CI 1.02-3.48, *P* = 0.042)	OR = 2.83 (95% CI 1.37-5.84, *P* = 0.004)	OR = 1.78 (95% CI 0.92-3.42, *P* = 0.092)	OR = 3.12 (95% CI 1.45-6.70, *P* = 0.003)
Handgrip strength < cutoff (AWGS 2019)	OR = 1.62 (95% CI 0.88-3.01, *P* = 0.122)	OR = 2.21 (95% CI 1.18-4.16, *P* = 0.013)	OR = 1.44 (95% CI 0.79-2.64, *P* = 0.233)	OR = 2.09 (95% CI 1.08-4.04, *P* = 0.028)
Gait speed < 1.0 m/s	OR = 1.72 (95% CI 0.94-3.14, *P* = 0.083)	OR = 1.91 (95% CI 1.05-3.46, *P* = 0.034)	OR = 1.59 (95% CI 0.86-2.95, *P* = 0.136)	OR = 2.27 (95% CI 1.15-4.48, *P* = 0.018)
Weight loss > 5%	OR = 1.84 (95% CI 0.92-3.69, *P* = 0.088)	OR = 2.63 (95% CI 1.32-5.23, *P* = 0.006)	OR = 1.88 (95% CI 0.92-3.85, *P* = 0.077)	OR = 2.71 (95% CI 1.29-5.68, *P* = 0.008)
Vitamin D (per 5 ng/mL increase)	OR = 0.84 (95% CI 0.68-1.04, *P* = 0.113)	OR = 0.78 (95% CI 0.63-0.97, *P* = 0.023)	OR = 0.86 (95% CI 0.70-1.06, *P* = 0.146)	OR = 0.73 (95% CI 0.58-0.93, *P* = 0.009)
Physical activity < 2 h/week	OR = 1.52 (95% CI 0.81-2.86, *P* = 0.192)	OR = 2.03 (95% CI 1.09-3.77, *P* = 0.025)	OR = 1.41 (95% CI 0.76-2.62, *P* = 0.272)	OR = 2.18 (95% CI 1.10-4.33, *P* = 0.026)

Abbreviations: OR = odds ratio; CI = confidence interval; AWGS = Asian Working Group for Sarcopenia; KOA = knee osteoarthritis.

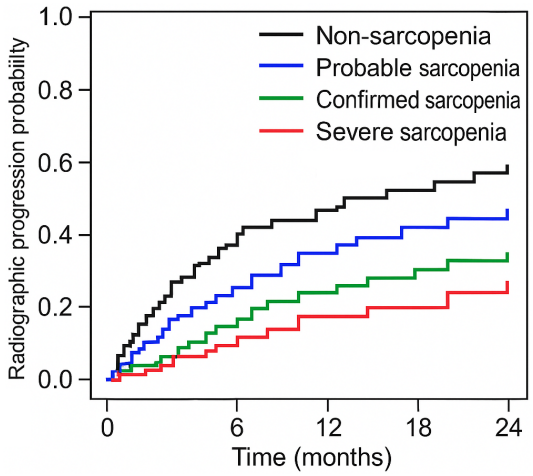

Figure 1. Kaplan-Meier analysis of radiographic progression by sarcopenia category. Cumulative probability curves show 24-month radiographic progression among non-sarcopenia, probable, confirmed, and severe sarcopenia groups.

differences amplify the detrimental effect of sarcopenia on joint deterioration.

Predictive-model performance and validation

As shown in **Figure 1**, the cumulative probability of radiographic KOA progression over the 24-month follow-up increased in a graded manner according to sarcopenia severity. Patients without sarcopenia exhibited the highest progression probability, whereas progressively lower probabilities were observed in the probable, confirmed, and severe sarcopenia groups. This stepwise separation of curves was evident early in follow-up and persisted throughout the observation period, indicating a time-dependent association between sarcopenia severity and radiographic progression risk (**Figure 1**). The final multivariate predictive model (**Table 6**), incorporating gait speed, phase angle, CRP, IL-6, albumin, and 25(OH)D, demonstrated strong discriminatory performance with an AUC of 0.86 (**Figure 2**). In contrast, sarcopenia severity alone provided only modest discrimination, yielding an AUC of 0.68 (**Figure 3**). Decision-curve analysis (DCA) also demonstrated clear differences in clinical utility. The sarcopenia-only model yielded minimal net benefit across most threshold probabilities, performing similarly to a "treat-none" strategy. Conversely, the multivariable model provided substantial net benefit over a broad threshold range (approximately 0.10-0.70), confirming its relevance for guiding individualized clinical decision-making in older adults with KOA (**Figures 2B** and **3B**). Furthermore, calibration analysis also supported the superiority of the multivariable model: the calibration curve for the sarcopenia-only model showed underestimation at low predicted probabilities and overestimation at higher predicted probabilities, indicating moderate calibration. In comparison, the multivariable model displayed excellent agreement between predicted and observed risks, with its calibration curve closely following the ideal 45° reference line, reflecting accurate probability estimation across risk strata (**Figures 2C** and **3C**). The multivariable prediction model demonstrated strong discriminative ability (**Figure 2A**), whereas sarcopenia severity alone showed only modest discrimination

Table 6. Predictive model for 24-month KOA progression (multivariate logistic regression)

Variable	β (SE)	Wald χ^2	OR (95% CI)	*p*-value
Phase angle (per 0.5° decrease)	0.49 (0.16)	9.45	1.63 (1.20-2.22)	0.002
Gait speed (per 0.1 m/s decrease)	0.59 (0.19)	9.62	1.81 (1.23-2.68)	0.002
CRP (per 1 mg/L increase)	0.22 (0.08)	7.61	1.25 (1.08-1.45)	0.006
IL-6 (per 1 pg/mL increase)	0.11 (0.04)	7.64	1.12 (1.03-1.22)	0.006
25(OH)D (per 5 ng/mL increase)	-0.08 (0.03)	6.92	0.92 (0.86-0.98)	0.009
Albumin (per 1 g/L increase)	-0.07 (0.03)	4.94	0.93 (0.88-0.99)	0.026
Constant	-1.38 (0.46)	9.02	-	0.003

Abbreviations: OR = odds ratio; CI = confidence interval; KOA = knee osteoarthritis.

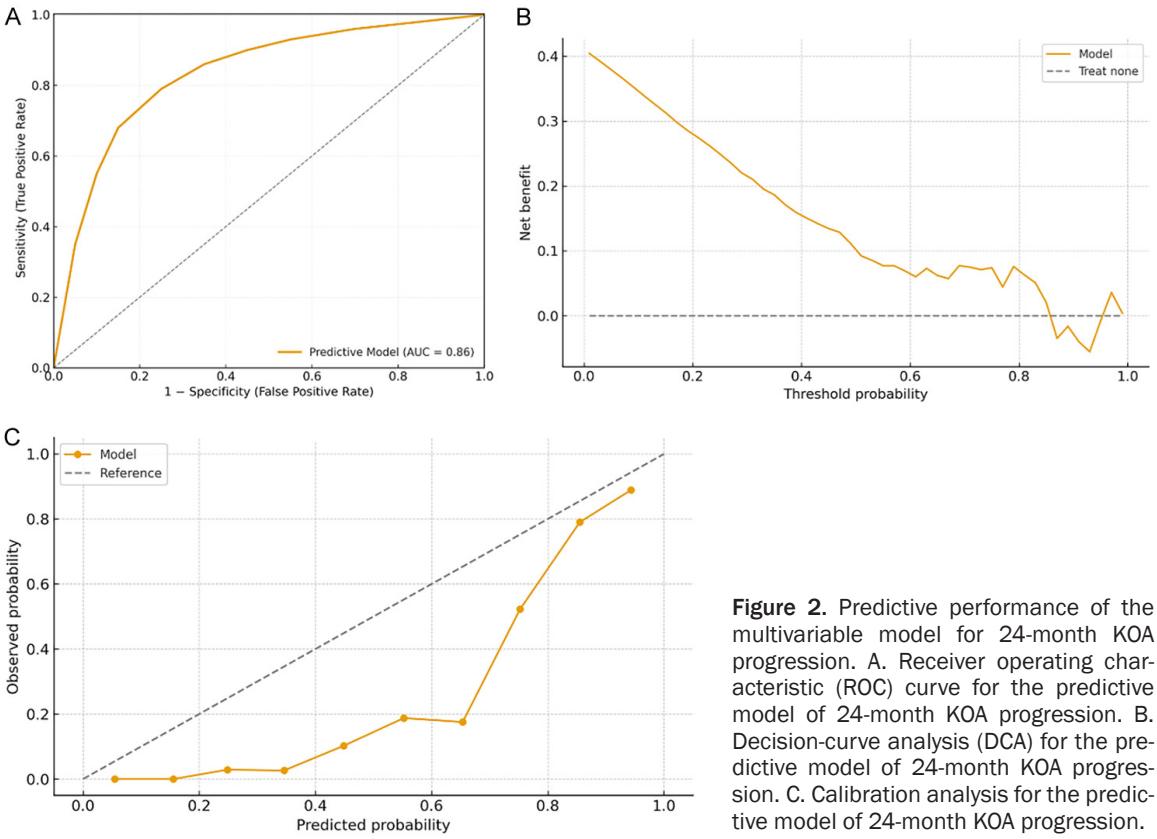

Figure 2. Predictive performance of the multivariable model for 24-month KOA progression. A. Receiver operating characteristic (ROC) curve for the predictive model of 24-month KOA progression. B. Decision-curve analysis (DCA) for the predictive model of 24-month KOA progression. C. Calibration analysis for the predictive model of 24-month KOA progression.

for radiographic progression (**Figure 3A**). The lower AUC of sarcopenia severity alone underscores the limited predictive capacity of single-domain muscle assessment and highlights the incremental value of combining functional, inflammatory, and nutritional indicators.

Consistent with these findings, adjusted ORs for radiographic progression increased progressively from probable to confirmed and severe sarcopenia, highlighting the graded prognostic impact of worsening muscle decline (**Figure 4**). Together, these discrimination, calibration, and DCA results indicate that the integration of functional, inflammatory, and nutritional indicators yields a markedly more robust and clinically useful prognostic tool than sarcopenia severity alone.

Based on the aforementioned analyses, the final multivariable predictive model (**Table 6**) consisted of six independent predictors as followings: logit(p) = -1.38 + 0.59 × (gait speed decrease per 0.1 m/s) + 0.49 × (phase angle decrease per 0.5°) + 0.22 × CRP + 0.11 × IL-6 - 0.07 × albumin - 0.08 × (25(OH)D per 5 ng/mL).

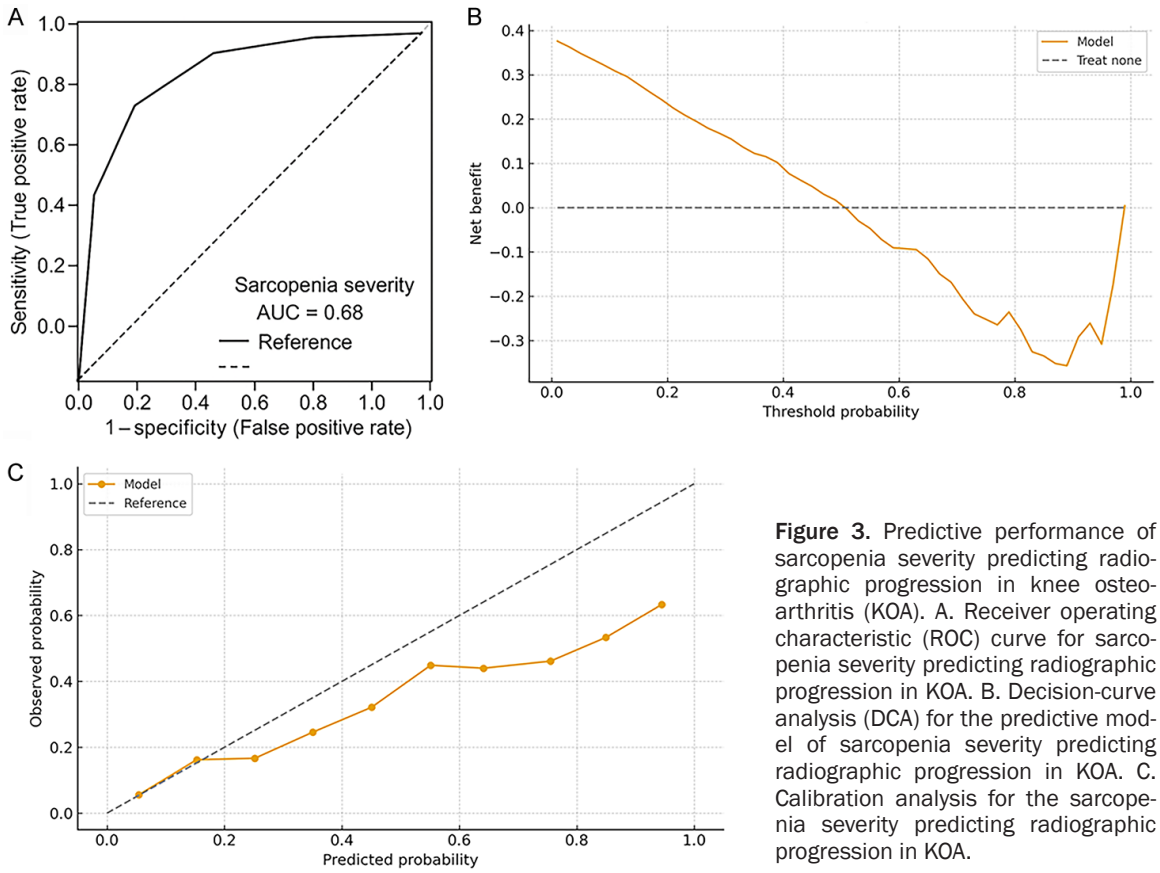

Figure 3. Predictive performance of sarcopenia severity predicting radiographic progression in knee osteoarthritis (KOA). A. Receiver operating characteristic (ROC) curve for sarcopenia severity predicting radiographic progression in KOA. B. Decision-curve analysis (DCA) for the predictive model of sarcopenia severity predicting radiographic progression in KOA. C. Calibration analysis for the sarcopenia severity predicting radiographic progression in KOA.

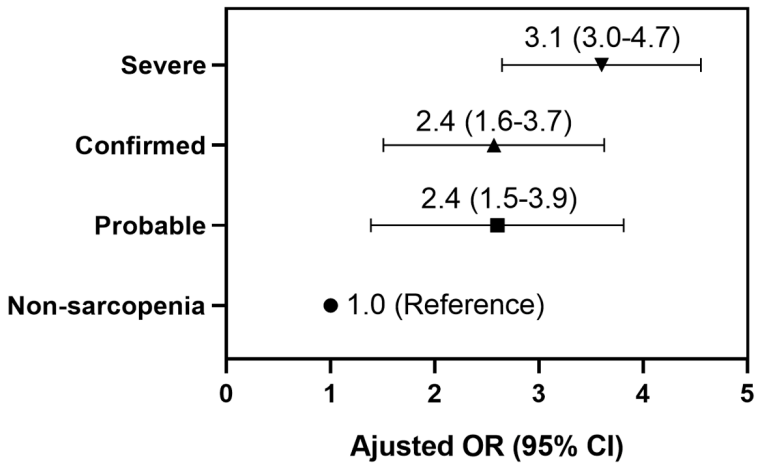

Figure 4. Association between sarcopenia severity and radiographic progression. Forest plot showing adjusted odds ratios (OR) and 95% confidence intervals (CI) for radiographic progression according to sarcopenia severity.

For demonstration, a patient with a 0.2 m/s decrease in gait speed, a 1.0° reduction in phase angle, CRP of 6 mg/L, IL-6 of 8 pg/mL, albumin of 38 g/L, and 25(OH)D of 18 ng/mL had a calculated linear predictor of 1.42, which was corresponding to a predicted 24-month radiographic progression probability of approximately 81%. The probability illustrated how the model integrates functional, inflammatory, and nutritional parameters to generate clinically interpretable risk estimates for the radiographic progression in KOA patients.

Discussion

The current study investigated the association between sarcopenia and the progression of KOA in older adults, and the findings highlighted that decreases in skeletal muscle mass and strength were strongly related to faster radiographic progression, aggravated pain, and reduced physical function. It was demonstrated that individuals with probable, confirmed, or severe sarcopenia experienced

significantly higher rates of KOA deterioration and functional impairment than non-sarcopenic participants, which suggests that sarcopenia is not only a comorbidity, but also an independent determinant of disease progression. Additionally, based on the 2019 AWGS criteria, our study also revealed a clear severity-dependent relationship between muscle decline and KOA progression: sarcopenia stage contributed to worsening radiographic deterioration, inflammatory activation, and nutritional depletion, supporting a dose-response association between sarcopenia severity and KOA progression.

Generally, sarcopenia and KOA frequently coexist in aging populations, and share similar risk factors such as advanced age, physical inactivity, obesity, and systemic inflammation [10, 16, 17]. Veronese et al. [10] demonstrated that lower-limb muscle strength and mass were independently associated with incident symptomatic KOA. A meta-analysis confirmed that low muscle mass index and sarcopenic obesity can increase KOA risk by 36% and 78%, respectively [16]. Similarly, a large Chinese longitudinal study indicated that sarcopenic obesity doubled the risk of KOA and that muscle strength mediated the effect of obesity on joint outcomes [17]. Our findings were consistent with these previous studies: beyond traditional anthropometric indicators, functional measures and biochemical indices independently predict structural progression. As shown in the logistic regression model, the integration of these variables achieved excellent discrimination and robust calibration, outperforming sarcopenia status alone, which suggests that combining inflammatory, nutritional, and biomechanical factors can enhance the precision of KOA prognosis.

The potential pathophysiological link between sarcopenia and KOA may be mediated via biomechanical, inflammatory, and metabolic mechanisms [6, 18-20]. Reduced quadriceps strength compromises joint stability, alters load distribution, and accelerates cartilage wear. Fat infiltration within skeletal muscle diminishes muscle contractility and promotes the release of proinflammatory cytokines such as IL-6 and TNF-α, which exacerbates chondrocyte catabolism and synovitis [21, 22]. Furthermore, sarcopenic obesity amplifies mechanical loading and systemic inflammation, creating a "vicious cycle" that drives progressive structural damage [23-25]. This interplay between mechanical stress and metabolic dysfunction underscores the dual importance of maintaining both muscle strength and metabolic health to mitigate KOA progression. Chronic low-grade inflammation may promote proteolysis and impair muscle regeneration, while hypovitaminosis D and hypoalbuminemia reflect poor anabolic reserve and reduced tissue repair capacity, jointly facilitating cartilage breakdown and joint space narrowing. Cross-sectional studies in U.S. and Asian populations have demonstrated independent associations between sarcopenia and the prevalence and severity of KOA after adjusting for age, sex, and BMI [6, 18]. Previous studies found that sarcopenic obesity was more strongly correlated with KOA severity than non-sarcopenic obesity [21]. Similarly, the JHPN cohort revealed that sarcopenic KOA patients exhibited higher pain scores and poorer performance on functional tests than their nonsarcopenic counterparts [18]. Recent Mendelian randomization analyses also provided genetic evidence for a causal relationship between reduced muscle mass and KOA, mediated in part by body fat mass [22]. Our subgroup analyses also showed that the impact of sarcopenia was particularly pronounced in women and in patients with varus malalignment. Together, these factors may magnify the detrimental consequences of muscle weakness on joint stability and cartilage integrity.

Muscle quality has emerged as another determinant of joint health. Thomas et al. [26] reported that reduced muscle radiodensity was associated with greater cartilage volume loss and functional decline, while Kalinkovich et al. [27] confirmed that sarcopenic obesity exacerbates inflammation and cartilage degeneration through adipokine dysregulation and mitochondrial dysfunction. In addition, our Kaplan-Meier analysis demonstrated that sarcopenia severity not only increased the likelihood of progression, but also accelerated its occurrence: patients with confirmed or severe sarcopenia showed earlier radiographic deterioration, implying that muscle loss may precipitate disease onset by reducing dynamic joint protection and neuromuscular coordination. This temporal relationship highlights the need for early

muscle-strengthening interventions in high-risk individuals.

Clinically, the integration of sarcopenia screening into KOA management offers valuable prognostic and therapeutic insights. The identification of sarcopenic or sarcopenic-obese phenotypes can guide personalized interventions to preserve muscle quality and joint integrity. Preoperative screening before TKA and perioperative strengthening may also reduce complications and improve recovery trajectories [16, 17]. These strategies align with the growing concept of "muscle-joint crosstalk", emphasizing the bidirectional influence between muscle degeneration and cartilage deterioration. Nevertheless, some limitations must be acknowledged. First, muscle assessment relied on bioelectrical impedance analysis or DXA rather than imaging-based muscle quality indices such as computed tomography or magnetic resonance imaging, which could underestimate myosteatosis. Second, while longitudinal data permit temporal inference, residual confounding from physical activity, nutrition, and systemic inflammation remains possible. Third, our study population primarily consisted of Asian elderly adults, so results may not fully generalize to other ethnicities. Future multicenter studies should combine imaging-based muscle phenotyping and randomized exercise-nutrition interventions to establish causality and refine treatment algorithms. Additionally, future studies should validate our findings in larger, multiethnic cohorts and explore whether correcting modifiable predictors can translate into slower radiographic progression.

In conclusion, sarcopenia significantly influences the onset and progression of KOA. Our data confirm that sarcopenia severity exerts a graded and time-dependent effect on KOA progression and that a multidimensional model incorporating inflammatory, nutritional, and biomechanical parameters enhances prognostic precision. Early identification and multimodal interventions should be prioritized to mitigate sarcopenia-related KOA progression. Recognizing the muscle-joint axis represents a critical step toward precision rehabilitation and healthier aging.

Disclosure of conflict of interest

None.

Address correspondence to: Tao Wen, Joint Surgery Department, Yangpu Hospital, School of Medicine, Tongji University, No. 450 Teng Yue Road, Yangpu District, Shanghai 200090, China. Tel: +86-158-21221505; E-mail: tw_yphtj24@outlook.com

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