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Reduced skeletal muscle independently predicts 1-year aggravated joint destruction in patients with rheumatoid arthritis

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Abstract

Background: Numerous cross-sectional studies have reported the associations between rheumatoid arthritis (RA) and reduced skeletal muscle. We firstly explored the dynamic change of skeletal muscle and its effect on RA clinical outcomes in a real-world prospective cohort.

Methods: Consecutive RA patients were treated according to the treat-to-target strategy and completed at least 1-year follow up. Clinical data and muscle index (assessed by bioelectric impedance analysis) were collected at baseline and visits at 3, 6, 9 and 12 months. Myopenia was defined by appendicular skeletal muscle mass index $\leqslant$7.0 kg/m^2 in men and $\leqslant$5.7 kg/m^2 in women. A 1-year radiographic progression as primary outcome was defined by a change in the total Sharp/van der Heijde modified score $\geqslant$0.5 units.

Results: Among 348 recruited patients, 315 RA patients (mean age 47.9 years, 84.4% female) completed 1-year follow up. There were 143 (45.4%) RA patients showing myopenia at baseline. Compared with those without baseline myopenia, RA patients with baseline myopenia had higher rate of 1-year radiographic progression (43.4% *versus* 21.5%, all $p < 0.05$). Baseline myopenia was an independent risk factor for 1-year radiographic progression with adjusted odds ratio (AOR) of 2.5-fold, especially among RA patients in remission at baseline both defined by Disease Activity Score in 28 joints (DAS28) including C-reactive protein (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR) with AOR of 18.5~42.9-fold. Further analysis of six subtypes of dynamic skeletal muscle change showed that newly acquired myopenia at endpoint was associated with radiographic progression (AOR of 5.4-fold).

Conclusions: Reduced skeletal muscle is an independent predicting factor for 1-year aggravated joint destruction, especially in remission RA. The importance of dynamic monitoring of skeletal muscle and muscle improvement therapy are worth exploration.

Keywords: joint destruction, radiographic progression, rheumatoid arthritis, skeletal muscle

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Introduction

Skeletal muscle is one of the most dynamic tissues in human body, comprising approximately 30–50% of total body weight and containing 50–75% of all body proteins.[1] Skeletal muscle contributes to multiple functions. It converts chemical into mechanical energy to generate power, maintain posture and produce movement, thus maintaining or enhancing health. Muscle mass depends on the balance between protein synthesis and degradation, and both processes are sensitive to many factors such as nutritional status, hormonal balance, physical activity, injury, chronic disease and inflammation. Of relevance to disease prevention and health maintenance, a reduced muscle mass impairs the body's ability to respond to stress and disease.[2,3] A new independent disease called sarcopenia was defined in 2016, referred to as

age-related loss of skeletal muscle function and muscle mass in older persons.[4] Compared with 'sarcopenia' for the elderly, 'myopenia' indicates the presence of clinically relevant muscle wasting due to any disease and at any age.[5] Sarcopenia/myopenia can result in reduced physical capability, quality of life, cardiopulmonary performance, and increased falls, fractures, disability and mortality, all with a high health cost.[6] These comorbidities are also found in patients with rheumatoid arthritis (RA) and result in worse outcomes.[7]

RA is a systemic inflammatory disease which combines joint inflammation and extra-articular manifestations.[8] Pain-related reduction in physical activity can result in reduced skeletal muscle.[9] More importantly, chronic inflammation itself can lead to a loss of muscle mass which is caused directly by cytokines including tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-17-driven hypermetabolism with an elevated rate of muscle protein loss.[10] Myopenia as reduced skeletal muscle was reported 13~57% in RA patients under different definitions.[9,11–13] Our previous cross-sectional study showed that RA patients ($n=457$) had higher prevalence of myopenia (45.1%) than age and sex-matched control subjects, and such myopenia was associated with joint damage.[14] Other cross-sectional studies reported the associations of decreased muscle mass with age, longer disease duration, greater disease activity, higher matrix metalloproteinase 3, low physical function, greater disability, osteoporosis and malnutrition.[9,11–13,15] However, few longitudinal studies on reduced skeletal muscle in RA have been reported. The dynamic change of skeletal muscle and its effect on RA clinical outcomes, including disease activity, physical function and joint destruction during the RA disease process remain elusive.

In this real-world prospective cohort study, we observed dynamic change of skeletal muscle and explored the influence of baseline reduced skeletal muscle and its dynamic change on RA clinical outcomes, with focus on 1-year joint damage progression. We identified high-risk models of different subtypes of skeletal muscle change with radiographic change during follow up.

Methods

Study design and participants

This study was designed as a real-world prospective cohort study conducted in Chinese patients with RA at Department of Rheumatology, Sun Yat-sen Memorial Hospital, Guangzhou, PR China, as described in our previous reports.[16,17] Consecutive RA patients aged ⩾16 years, who fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA[18] were recruited from August 2015 to April 2018. Exclusion criteria included overlapping other autoimmune diseases (e.g. systemic lupus erythematosus, scleroderma, dermatomyositis, etc.), malignancy, serious infection, organ dysfunction including hepatic, renal and respiratory dysfunction, pregnancy, severe mental disorders, implanted electronic devices and patients' request for exclusion. All patients were treated according to the 2013/2016 EULAR recommendations of 'treat-to-target' strategy and completed at least 1-year follow up. The therapeutic target was defined as Disease Activity Score in 28 joints with four variables including C-reactive protein (DAS28-CRP) <2.6 in all patients or <3.2 in patients with long disease duration (>24 months).[19,20] This study was conducted in compliance with the Helsinki Declaration and the protocol was approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital (SYSEC-2009-06 and SYSEC-KY-KS-012). All participants gave their written informed consent before clinical data collection.

Data collection

Available demographic and clinical data were collected at baseline and visits at 3, 6, 9 and 12 months, as described before[16,17] and modified according to 2017 EULAR recommendation.[21] Demographic data included age, sex, smoking habits and body mass index (BMI). BMI (kg/m^2) was calculated as weight (kg) divided by height (m) squared. Weight was measured to the nearest 0.1 kg without shoes, socks, bulky clothing and other accessories. Height was measured to the nearest 0.01 m without shoes and socks using a stadiometer.

Clinical data included disease duration, time of morning stiffness, 28-joint tender and swollen joint count (28TJC and 28SJC), patient and provider global assessment of disease activity (PtGA and PrGA, respectively, range 0–10 cm), pain visual analogue scale (pain VAS, range 0–10 cm), erythrocyte sedimentation rate [ESR, normal range 0–20 mm/h (female), 0–15 mm/h (male)], CRP (normal range 0–5 mg/l), rheumatoid factor

(RF, normal range 0–20 mg/l), determined by nephelometry (Siemens Healthcare Diagnostics, Munich, Germany), anti-cyclic citrullinated peptide antibody (ACPA, normal range 0–18 IU/ml, measured by enzyme-linked immunosorbent assay (Aesku Diagnostics, Wendelsheim, Germany), medications and comorbidities. Disease activity was assessed with DAS28-CRP, Disease Activity Score in 28 joints including ESR (DAS28-ESR), simplified disease activity index (SDAI) and clinical disease activity index (CDAI). Disease activity defined by DAS28-CRP or DAS28-ESR was divided into four categories: high disease activity (DAS28 >5.1), moderate disease activity ($3.2 \leqslant$DAS28 $\leqslant 5.1$), low disease activity ($2.6 \leqslant$DAS28 <3.2) and remission (DAS28 <2.6). Active RA was defined as DAS28 $\geqslant 2.6$.[8] A Chinese language version of the Stanford Health Assessment Questionnaire (HAQ) was used to assess physical activity function in eight categories (dressing, rising, eating, walking, hygiene, reaching, griping and activities). Cumulative doses of oral glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) were recorded during 1-year follow up. Steroid doses were converted to a prednisone-equivalent dose.

Conventional radiographs of bilateral hands and wrists (anteroposterior view) of all RA patients were collected at baseline and 12 months. Radiographs were assessed according to the Sharp/van der Heijde modified score,[22] using the average scores of two experienced readers (YZH from Radiology and CLF from Rheumatology) who were blinded to clinical data as we described previously.[16,17] A total of 16 areas for joint erosion and 15 for joint-space narrowing (JSN) of the hands were assessed in each hand/wrist. The maximum score per single joint for erosion is 5, and for JSN is 4, with the sum of erosion (0–160) and JSN (0–120) subscores constituting modified total Sharp score (mTSS, 0–280). The mean intra-class correlation coefficient for inter-examiner agreement was 0.945.

Exposure

Body composition (BC) was assessed at baseline and visits at 3, 6, 9 and 12 months by bioelectric impedance analysis (BIA) using an InBody 230 device (Biospace Co., Shanghai, China), which included fat-free mass, fat mass, body fat percentage (BF%), the mass and distribution of muscle and fat in trunk and appendicular extremities.[23] Appendicular skeletal muscle mass index (ASMI) was calculated as appendicular skeletal muscle mass/height^2 (kg/m^2). Myopenia was defined by ASMI $\leqslant 7.0$ kg/m^2 in men and $\leqslant 5.7$ kg/m^2 in women according to the Asian Working Group for Sarcopenia (AWGS).[24] The primary exposure was baseline myopenia.

According to baseline and dynamic skeletal muscle change from baseline to 12 months, all RA patients were divided into six subtypes: in baseline non-myopenia patients, those experiencing an ASMI increase (ΔASMI >0) and non-myopenia at endpoint (subtype 1), an ASMI decrease (ΔASMI $\leqslant 0$) but also non-myopenia at endpoint (subtype 2) and an ASMI decrease to myopenia at endpoint (subtype 3); in baseline myopenia patients, those experiencing an ASMI increase to non-myopenia at endpoint (subtype 4), an ASMI increase but also myopenia at endpoint (subtype 5) and an ASMI decrease and myopenia at endpoint (subtype 6).

Outcome

The primary outcome was 1-year radiographic progression defined as a change in modified total Sharp score (ΔmTSS) $\geqslant 0.5$ units from baseline to 12 months.[25]

Statistical analysis

Statistical analyses were performed with SPSS for Windows 20.0 statistical software (IBM, Armonk, NY, USA). There were no missing data in primary exposure and outcome, and missing data of clinical indicators at 3, 6 or 9 months were not imputed because of no influence on the effect on primary exposure and primary outcome in our study. Data were presented as frequencies and percentages for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables according to distributions. The two independent samples *t*-test or Mann–Whitney test were used to compare the differences of continuous variables according to distributions between two groups with or without exposure. Chi-square test or Fisher's exact test were used for categorical variables in the two groups. The mixed-effect model was used to compare the differences of dynamic indicators of disease activity and function between the two groups. The two independent samples *t*-test or Mann–Whitney test were also used to compare the differences of dynamic indicators of disease activity and function between

two groups with or without exposure at baseline, 3, 6, 9 and 12 months, respectively. The two paired samples *t*-test was used for ASMI at 3, 6, 9 and 12 months compared with baseline in all RA patients and those with or without exposure at baseline. The Kruskal–Wallis test or chi-square test was used for comparison in six subtypes of dynamic skeletal muscle change. The Bonferroni correction was used for multiple comparisons in six subgroups. All significance tests were two-tailed and were conducted at the 5% significance level.

Logistic-regression analyses were used to identify the relationship between primary exposure and primary outcome in all RA patients, those with active RA and those in remission at baseline, and the relationship between subtypes of muscle change and primary outcome, by calculating odds ratio (OR) and adjusted OR (AOR). Potential confounders were adjusted in AOR regression a ([a]AOR) including age, sex, smoking habits, BMI, BF%, disease duration, RF status, ACPA status, DAS28-CRP, Health Assessment Questionnaire Disability Index (HAQ-DI), mTSS, hypertension, type 2 diabetes and dyslipidemia at baseline, and 1-year cumulative doses of medications including steroids, conventional synthetic DMARDs (csDMARDs) and biologic agents. The same confounders were adjusted in AOR regression b ([b]AOR) with substituting DAS28-ESR for DAS28-CRP.

Results

Baseline characteristics of all RA patients

Among 348 recruited RA patients, 33 were excluded for various reasons. Sixteen patients requested exclusion for long travel, migration to other provinces or rejection of treatment adjustment under 'treat-to-target' strategy. Eight patients were excluded for loss of follow up, three patients for pregnancy, three patients for overlapping systemic lupus erythematosus after entry, three patients for cancer, including one nasopharyngeal carcinoma diagnosed at 4 months, one breast cancer diagnosed at 8 months, and one lung cancer diagnosed at 10 months (Figure 1). At the end, 315 RA patients who completed 1-year follow up were included for statistical analysis. Their baseline characteristics are shown in Table 1. Mean age was 47.9 ± 12.4 years, with 266 (84.4%) female. Median disease duration was 49 (IQR 24–98) months, 5.1% with short disease duration (<6 months), and 72.7% with long disease duration (>24 months). According to DAS28-CRP, there were 15.6% RA patients with high, 35.2% moderate, 11.4% low disease activity and 37.8% in remission. According to DAS28-ESR, there were 26.7% RA patients with high, 34.9% moderate, 13.0% low disease activity and 25.4% in remission. There were 20.0% patients without previous steroids or DMARD therapy for 6 months before enrolment (treatment naïve). There were 44 (14.0%) RA patients with hypertension, 17 (5.4%) with type 2 diabetes and 23 (7.3%) with dyslipidemia.

Clinical characteristics of RA patients with baseline myopenia

There were 143 (45.4%) RA patients with baseline myopenia and their clinical characteristics at baseline are shown in Table 1. Compared with those without, RA patients with baseline myopenia had longer disease duration (median 72 *versus* 47 months, $p = 0.020$), higher pain VAS (median 3 *versus* 2 cm, $p = 0.007$), worse functional indicators including HAQ-DI (median 0.25 *versus* 0.13, $p = 0.003$) and the rate of physical dysfunction (39.9% *versus* 26.7%, $p = 0.013$), higher radiographic assessment index including mTSS (median 16.5 *versus* 6.0, $p < 0.001$), JSN subscore (median 7.0 *versus* 1.0, $p < 0.001$) and erosion subscore (median 7.0 *versus* 4.0, $p = 0.001$).

Most RA patients improved after treatment during 1-year follow up (Supplemental Figure S1). Compared with those without, RA patients with baseline myopenia had significantly higher disease activity indicators at 12 months including 28TJC (median 1 *versus* 0, $p = 0.034$), PtGA (median 2 *versus* 1 cm, $p = 0.010$), PrGA (median 2 *versus* 1 cm, $p = 0.010$), pain VAS (median 2 *versus* 1 cm, $p = 0.001$), DAS28-CRP (median 2.51 *versus* 1.99, $p = 0.009$), DAS28-ESR (median 3.00 *versus* 2.59, $p = 0.018$), SDAI (median 6.31 *versus* 3.35, $p = 0.006$) and CDAI (median 6 *versus* 2, $p = 0.007$), as well as higher HAQ-DI at each visit (median 0.13 *versus* 0, all $p < 0.01$). Mixed-effect-model analysis also showed that compared with those without, RA patients with baseline myopenia had significantly higher disease activity indicators, including PtGA, PrGA, pain VAS, CRP, DAS28-CRP, SDAI, CDAI and HAQ-DI, during 1-year follow up (all $p < 0.05$). There was no significant difference between two groups in initial therapy as well as both six-month and 1-year cumulative

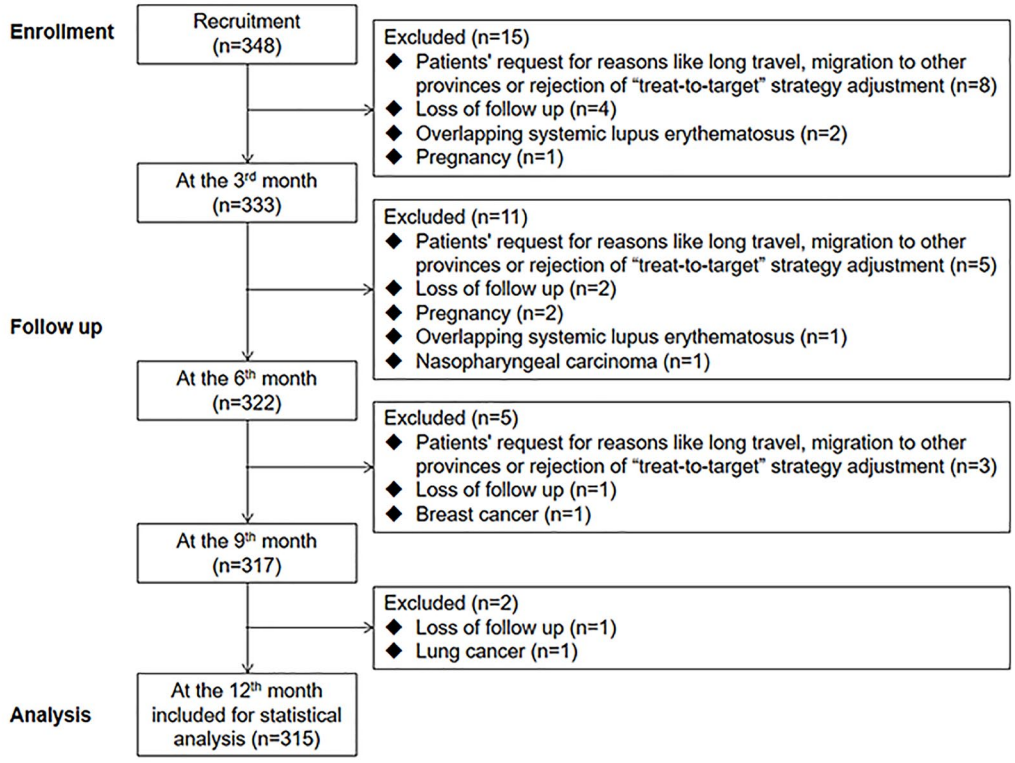

Figure 1. Flow diagram of RA patients during 1-year follow up.
RA, rheumatoid arthritis.

doses of steroids and DMARDs after enrolment (all $p > 0.05$, Supplemental Table S1).

Association between baseline myopenia and 1-year radiographic progression

There were 99 (31.4%) RA patients showing 1-year radiographic progression. Compared with those without, RA patients with baseline myopenia showed significantly higher rate of radiographic progression (43.4% *versus* 21.5%, $p < 0.001$, Table 2). The cumulative probability distribution of radiographic change from baseline to 12 months in both groups and the difference between the curves of the two groups showed that the myopenia group had higher ΔmTSS, ΔJSN subscore and Δerosion subscore, and higher proportion of 1-year radiographic progression (all $p < 0.01$, Figure 2). Univariate logistic-regression analysis showed that baseline myopenia was associated with a significantly higher likelihood of 1-year radiographic progression [OR = 2.793, 95% confidence interval (CI): 1.708–4.566, $p < 0.001$]. After adjustment for potential confounders including age, sex, smoking, BMI, BF%, disease duration, RF status, ACPA status, DAS28-CRP, HAQ-DI, mTSS, hypertension, type 2 diabetes and dyslipidemia at baseline, and 1-year cumulative doses of medications including steroids, csDMARDs and biologic agents, multivariate logistic-regression analysis confirmed that baseline myopenia was an independent risk factor associated with 1-year radiographic progression ([a]AOR = 2.461, 95% CI: 1.083–5.591, $p = 0.032$). Further adjustment for the same potential confounders with substituting DAS28-ESR for DAS28-CRP, baseline myopenia was also associated with 1-year radiographic progression ([b]AOR = 2.452, 95% CI: 1.080–5.565, $p = 0.032$, Table 2).

According to DAS28-CRP, there were 67 (34.2%) patients with active RA at baseline and 32 (26.9%) RA patients in remission at baseline, with a 1-year radiographic progression respectively. Among the patients with active RA at baseline, those with baseline myopenia showed significantly higher rate of radiographic progression than those without (46.2% *versus* 23.3%, $p = 0.001$). Among the RA patients in remission at baseline, those with baseline myopenia also showed significantly higher rate of radiographic progression than

Table 1. Demographic and clinical characteristics of RA patients at baseline.

Indicators	All patients (*n* = 315)	Baseline non-myopenia (*n* = 172)	Baseline myopenia (*n* = 143)	*p**
Age, years, mean ± SD	47.9 ± 12.4	47.6 ± 10.8	48.2 ± 14.2	0.686
Female, *n* (%)	266 (84.4)	146 (84.9)	120 (83.9)	0.813
Smoking, *n* (%)	42 (13.3)	22 (12.8)	20 (14.0)	0.756
BMI, kg/m^2, mean ± SD	21.9 ± 3.4	23.5 ± 3.1	19.9 ± 2.4	**<0.001**
ASMI, kg/m^2, mean ± SD	6.0 ± 0.9	6.5 ± 0.7	5.4 ± 0.6	**<0.001**
Disease duration, months, median (IQR)	49 (24–98)	47 (20–84)	72 (25–120)	**0.020**
Morning stiffness, min, median (IQR)	0 (0–10)	0 (0–10)	0 (0–15)	0.371
28TJC, median (IQR)	2 (0–5)	2 (0–4)	2 (0–7)	0.114
28SJC, median (IQR)	1 (0–4)	1 (0–4)	2 (0–5)	0.372
PtGA, cm, median (IQR)	3 (1–5)	2 (0–5)	3 (1–5)	0.084
PrGA, cm, median (IQR)	3 (1–5)	2 (0–5)	3 (1–5)	0.056
Pain VAS, cm, median (IQR)	2 (1–4)	2 (1–4)	3 (2–4)	**0.007**
ESR, mm/h, median (IQR)	31 (15–50)	27 (17–43)	32 (15–55)	0.306
CRP, mg/l, median (IQR)	4.8 (3.3–18.1)	5.4 (3.3–13.0)	4.3 (3.3–24.3)	0.516
Positive RF, *n* (%)	215 (68.3)	122 (70.9)	93 (65.0)	0.263
Positive ACPA, *n* (%)	221 (70.2)	127 (73.8)	94 (65.7)	0.118
DAS28-CRP, median (IQR)	3.3 (2.1–4.5)	3.0 (2.0–4.3)	3.5 (2.1–4.7)	0.124
DAS28-ESR, median (IQR)	3.8 (2.6–5.2)	3.6 (2.5–5.0)	4.0 (2.6–5.5)	0.204
SDAI, median (IQR)	10.4 (4.1–22.2)	8.8 (3.3–20.9)	13.3 (4.3–23.2)	0.083
CDAI, median (IQR)	10 (3–20)	8 (2–19)	12 (4–20)	0.110
HAQ-DI, median (IQR)	0.13 (0–0.63)	0.13 (0–0.50)	0.25 (0–0.88)	**0.003**
JSN subscore, median (IQR)	3.5 (0–14.0)	1.0 (0–8.0)	7.0 (1.5–19.0)	**<0.001**
Erosion subscore, median (IQR)	5.0 (1.0–17.5)	4.0 (1.0–11.9)	7.0 (2.0–24.0)	**0.001**
mTSS, median (IQR)	9.5 (2.0–30.0)	6.0 (1.5–21.9)	16.5 (5.0–38.0)	**<0.001**
Previous medications				
Treatment naïve$^{\Delta}$, *n* (%)	63 (20.0)	35 (20.3)	28 (19.6)	0.865
Steroids, *n* (%)	165 (52.4)	86 (50.0)	79 (55.2)	0.353
csDMARDs, *n* (%)	234 (74.3)	131 (76.2)	103 (72.0)	0.403
Biologic agents, *n* (%)	39 (12.4)	16 (9.3)	23 (16.1)	0.069
Comorbidities				
Hypertension, *n* (%)	44 (14.0)	22 (12.8)	22 (15.4)	0.508
Type 2 diabetes, *n* (%)	17 (5.4)	10 (5.8)	7 (4.9)	0.719
Dyslipidemia, *n* (%)	23 (7.3)	14 (8.1)	9 (6.3)	0.531

*Comparisons between patients with and without baseline myopenia.
$^{\Delta}$Treatment naïve, without previous steroids or DMARD therapy for 6 months before enrolment.
Bolded numerals indicate statistical significance.
ACPA, anti-cyclic citrullinated peptide antibody; ASMI, appendicular skeletal muscle mass index; BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; IQR, interquartile range; JSN, joint-space narrowing; mTSS, modified total Sharp score; PrGA, provider global assessment of disease activity; PtGA, patient global assessment of disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Table 2. Association between baseline myopenia and 1-year radiographic progression in RA patients.

Outcome	Baseline non-myopenia	Baseline myopenia	*p*
All RA patients			
n	172	143	
Non-radiographic progression, *n* (%)	135 (78.5)	81 (56.6)	**<0.001**
Radiographic progression, *n* (%)	37 (21.5)	62 (43.4)	
OR (95% CI)	Ref	**2.793 (1.708–4.566)**	**<0.001**
[a]AOR (95% CI)	Ref	**2.461 (1.083–5.591)**	**0.032**
[b]AOR (95% CI)	Ref	**2.452 (1.080–5.565)**	**0.032**
Baseline DAS28-CRP			
Active			
n	103	93	
Non-radiographic progression, *n* (%)	79 (76.7)	50 (53.8)	**0.001**
Radiographic progression, *n* (%)	24 (23.3)	43 (46.2)	
OR (95% CI)	Ref	**2.831 (1.535–5.222)**	**0.001**
[a]AOR (95% CI)	Ref	1.532 (0.565–4.155)	0.402
Remission			
n	69	50	
Non-radiographic progression, *n* (%)	56 (81.2)	31 (62.0)	**0.020**
Radiographic progression, *n* (%)	13 (18.2)	19 (38.0)	
OR (95% CI)	Ref	**2.640 (1.150–6.060)**	**0.022**
[a]AOR (95% CI)	Ref	**18.471 (2.277–149.860)**	**0.006**
Baseline DAS28-ESR			
Active			
n	127	108	
Non-radiographic progression, *n* (%)	97 (76.4)	59 (54.6)	**<0.001**
Radiographic progression, *n* (%)	30 (23.6)	49 (45.4)	
OR (95% CI)	Ref	**2.685 (1.537–4.691)**	**0.001**
[b]AOR (95% CI)	Ref	1.951 (0.782–4.869)	0.152
Remission			
n	45	35	
Non-radiographic progression, *n* (%)	38 (84.4)	22 (62.9)	**0.027**
Radiographic progression, *n* (%)	7 (15.6)	13 (37.1)	
OR (95% CI)	Ref	**3.208 (1.113–9.243)**	**0.031**
[b]AOR (95% CI)	Ref	**42.864 (1.277–1438.994)**	**0.036**

Active RA, DAS28-CRP ⩾2.6; remission, DAS28-CRP <2.6.
[a]AOR: adjusted for age, sex, smoking habits, BMI, BF%, disease duration, RF status, ACPA status, DAS28-CRP, HAQ-DI, mTSS, hypertension, type 2 diabetes and dyslipidemia at baseline and 1-year cumulative doses of medications including steroids, csDMARDs and biologic agents.
[b]AOR: adjusted for the same confounders in [a]AOR, substituting DAS28-ESR for DAS28-CRP.
Bolded numerals indicate data with statistical significance.
95% CI, 95% confidence interval; ACPA, anti-cyclic citrullinated peptide antibody; AOR, adjusted odds ratio; BF, body fat; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP, Disease Activity Score in 28 joints including C-reactive protein; DAS28-ESR, Disease Activity Score in 28 joints including erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, modified total Sharp score; OR, odds ratio; RA, rheumatoid arthritis; Ref, reference; RF, rheumatoid factor.

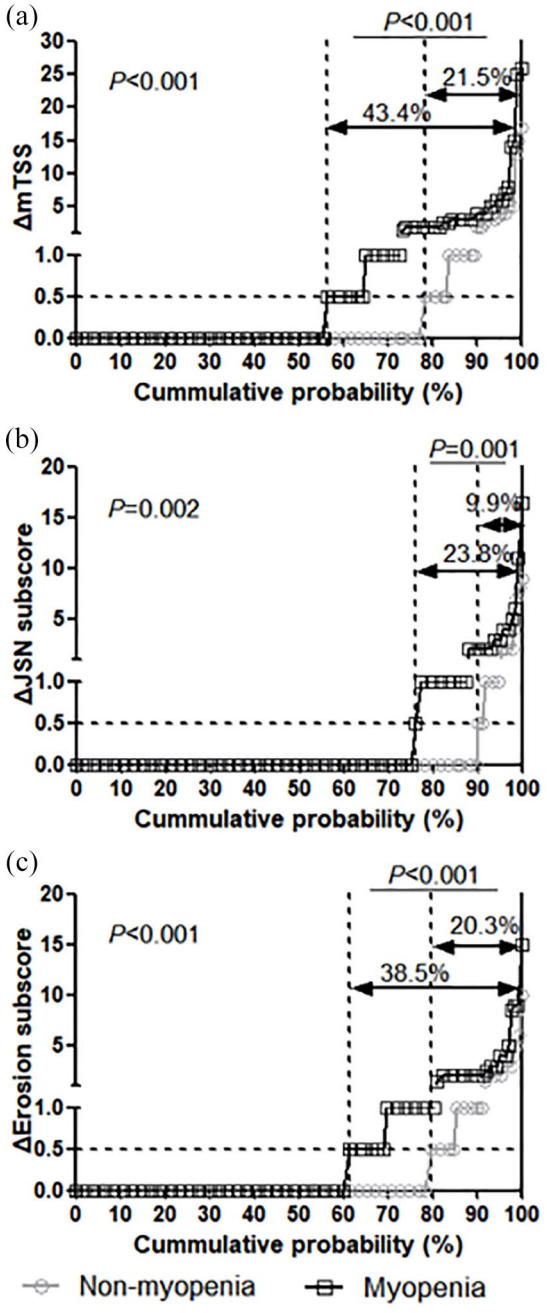

Figure 2. Comparisons of radiographic change from baseline to 12 months between RA patients with and without baseline myopenia.
ΔErosion subscore, a change in erosion subscore from baseline to 12 months; ΔJSN subscore, a change in joint-space narrowing subscore from baseline to 12 months; ΔmTSS, a change in modified total Sharp score from baseline to 12 months; RA, rheumatoid arthritis.

those without (38.0% *versus* 18.2%, $p = 0.020$). Univariate and multivariate logistic-regression analysis confirmed that in remission at baseline, baseline myopenia was an independent risk factor of 1-year radiographic progression ([a]AOR = 18.471, 95% CI: 2.277–149.860, $p = 0.006$, Table 2).

According to DAS28-ESR, there were 79 (33.6%) patients with active RA at baseline and 20 (25.0%) RA patients in remission at baseline, with a 1-year radiographic progression, respectively. Among the patients with active RA at baseline, those with baseline myopenia showed significantly higher rate of radiographic progression than those without (45.4% *versus* 23.6%, $p < 0.001$). Among the RA patients in remission at baseline, those with baseline myopenia also showed significantly higher rate of radiographic progression than those without (37.1% *versus* 15.6%, $p = 0.027$). Univariate and multivariate logistic-regression analysis confirmed that in remission at baseline, baseline myopenia was an independent risk factor of 1-year radiographic progression ([b]AOR = 42.864, 95% CI: 1.277–1438.994, $p = 0.036$, Table 2).

Associations between subtypes of muscle change and 1-year radiographic progression

Compared with baseline [$5.96 \pm 0.86\,kg/m^2$, Figure 3(a)], ASMI in all RA patients increased at 3 months ($6.00 \pm 0.84\,kg/m^2$), 6 months ($6.01 \pm 0.83\,kg/m^2$), 9 months ($6.00 \pm 0.84\,kg/m^2$), and 12 months ($5.99 \pm 0.87\,kg/m^2$), especially in those with baseline myopenia [Figure 3(b)]. During the 1-year follow up, there were 41.6%~45.4% RA patients with myopenia, ASMI increased in 165 (52.4%) RA patients after treatment but decreased in 130 (41.3%) patients and remained stable in 20 (6.3%) patients. There were 16.8% patients with baseline myopenia turned to endpoint non-myopenia, and 9.3% patients without baseline myopenia that developed myopenia at 12 months [Figure 3(c)].

Further subgrouping according to baseline and dynamic skeletal muscle change [Figure 3(d)] showed that there were 82 (26.0%) patients with subtype 1 (no myopenia at baseline with increased muscle mass), 74 (23.5%) with subtype 2 (no myopenia at baseline with slightly decreased muscle mass), 16 (5.1%) with subtype 3 (no myopenia at baseline but myopenia at endpoint), 24 (7.6%) with subtype 4 (myopenia at baseline but no myopenia at endpoint), 59 (18.7%) with subtype 5 (myopenia at baseline with slightly increased muscle mass), and 60 (19.0%) with subtype 6 (myopenia at baseline with decreased muscle mass). When comparing clinical

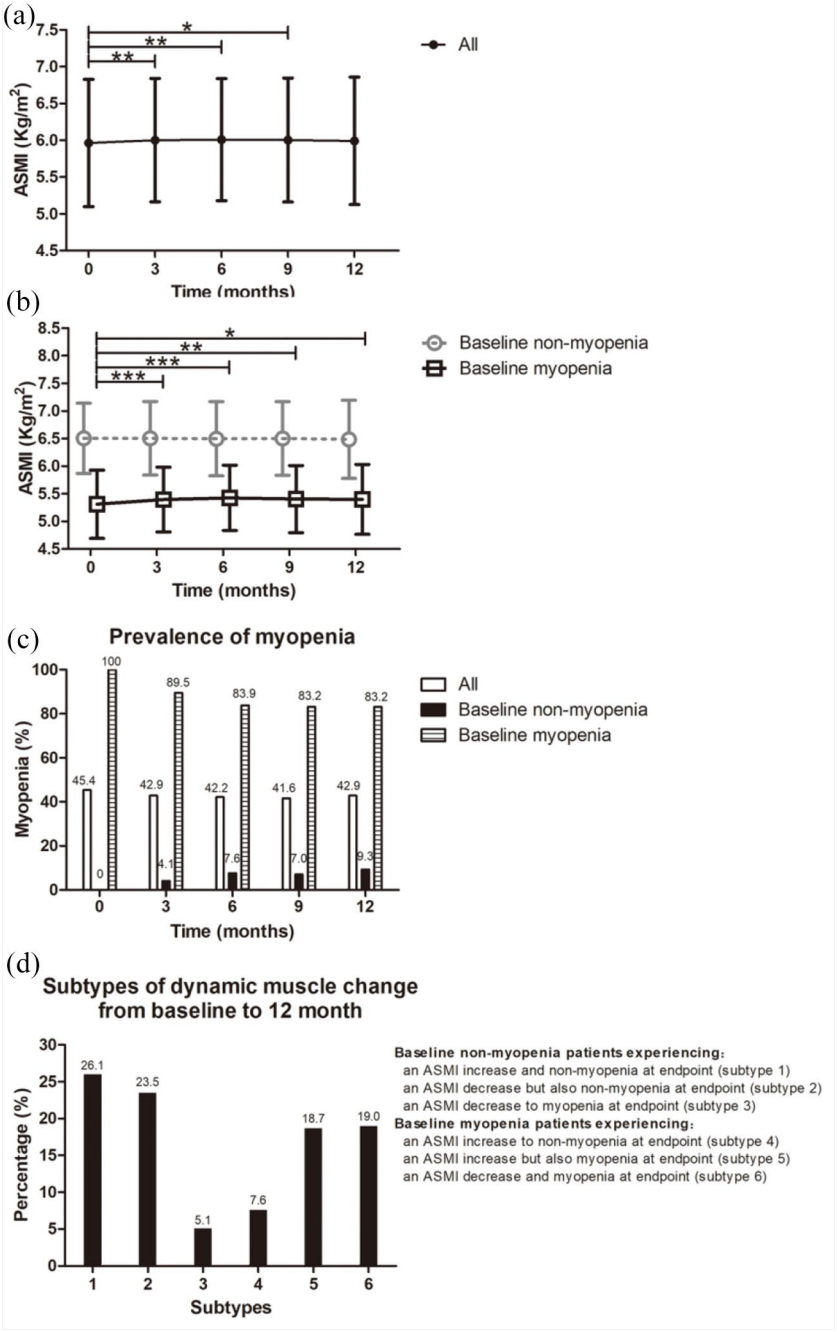

Figure 3. ASMI, myopenia and subtypes of dynamic skeletal muscle change in RA patients from baseline to 12 months.

Compared with baseline, ASMI increased in all RA patients (a) and those with baseline myopenia at 3, 6, 9 and 12 months (b), with their prevalence of myopenia (c) and subtypes of dynamic skeletal muscle change from baseline to 12 months (d).

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

ASMI, appendicular skeletal muscle mass index; RA, rheumatoid arthritis.

indicators during 1-year follow up among the six subtypes, subtype 1 showed a trend of the best controlled disease indicators, with subtype 3 showing a trend of the worst control (remission rate at 12 month: 73.2%, 59.5%, 43.8%, 50.0%, 62.7%, and 45.0% in subtype 1–6 respectively, $p = 0.013$ for comparison in six groups, but all $p > 0.0033$ with Bonferroni correction for

multiple comparisons, data not shown), although there was no significant difference among the six subtypes. There was no significant difference among the six groups regarding initial therapy and 1-year cumulative doses of steroids and DMARDs after enrolment, except that subtype 5 showed lower 1-year cumulative doses of methotrexate than subtype 1 (Supplemental Table S2).

Among the six subtypes, RA patients with subtype 1 showed the lowest rate of 1-year radiographic progression with 17.1%, while subtype 3 had the highest rate with 50.0% (Table 3). Univariate logistic-regression analysis showed that subtypes 3, 5 and 6 were related to 1-year radiographic progression compared with subtype 1. After adjustment for potential confounders, multivariate logistic-regression analysis confirmed these results of subtype 3 ([a]AOR = 5.402, 95% CI: 1.491–19.576; [b]AOR = 5.398, 95% CI: 1.492–19.535), subtype 5 ([a]AOR = 4.161, 95% CI: 1.207–14.342; [b]AOR = 4.179, 95% CI: 1.211–14.415) and subtype 6 ([a]AOR = 4.891, 95% CI: 1.668–14.345; [b]AOR = 4.904, 95% CI: 1.671–14.395).

Discussion

This is the first longitudinal study investigating the relationship between dynamic skeletal muscle change, especially baseline reduced skeletal muscle and RA clinical outcomes during 1-year follow up, and the key findings were the link to joint destruction and the identification of related-risk individuals based on skeletal muscle assessment. RA patients with baseline myopenia had a higher rate of radiographic progression than those without (43.4% *versus* 21.5%). Baseline myopenia was an independent risk factor for 1-year radiographic progression (AOR of 2.5-fold). This was even more impressive in RA patients in remission at baseline both defined by DAS28-CRP or DAS28-ESR, of whom those with baseline myopenia showed a higher risk of radiographic progression (AOR of 18.5~42.9-fold). Moreover, our data firstly revealed the dynamic changes of skeletal muscle in a large RA cohort during 1-year follow up which were classified into six subtypes. RA patients with newly acquired myopenia at 1 year was associated with radiographic progression (AOR of 5.4-fold) who were the highest-risk individuals among six subtypes. All these findings indicate that reduced skeletal muscle is an independent predicting factor for 1-year radiographic progression especially in remission RA.

RA is characterized by elevation of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-17, all involved in bone destruction. The same cytokines might also facilitate muscle loss through the suppression of myogenic proliferation and differentiation, combined with muscle degradation.[26] TNF-α can also affect skeletal muscle function through suppressing muscle fibre contractility.[27] A recent research on human myoblasts showed that TNF-α and/or IL-17 promote IL-6 secretion in myoblasts, with increased endoplasmic reticulum and mitochondrial stress. The resulting calcium accumulation in myoblasts affects muscle-cell contractibility, indicating that inflammatory cytokines can induce muscle-cell dysfunction.[28] Decreased muscle mass has already been found in active RA with high-grade inflammation.[29] Significant gain in skeletal muscle mass was reported in 21 RA patients treated with tocilizumab (a humanized anti-IL-6 receptor antibody) for 1 year in a longitudinal study.[30] In our real-world 1-year prospective study, the mean ASMI in all RA patients increased, accompanied with disease activity improvement after 'treat-to-target strategy' treatment, especially in those with baseline myopenia. Moreover, this larger cohort allowed further classification as six subtypes of dynamic skeletal muscle changes and firstly highlighted RA patients with newly acquired myopenia at 1 year as the highest-risk subtype with the worst radiographic outcome.

The relationship between muscle and bone remains incompletely understood. More recent cross-sectional studies revealed the association of decreased skeletal muscle with lower bone mineral density,[9,31] osteoporosis,[32,33] bone erosion[34] and joint destruction.[9,14] Systemic inflammation in RA is thought to be a pathogenesis link between muscle wasting and bone loss. Our longitudinal data extends the association between reduced skeletal muscle and joint damage. Among RA patients in remission at baseline, an increased risk of 18.5~42.9-fold for joint damage progression was found in those with baseline myopenia *versus* those without, which implies some cross-talk rather than systemic inflammation between muscle and bone. Recently, we reported that increased nuclear accumulation of a metabolic transcription factor peroxisome proliferator-activated receptor γ coactivator 1β (PGC1β) in circulating osteoclast precursors from RA patients promoted osteoclastogenesis and was associated with bone destruction.[35] The study of skeletal-muscle-specific PGC1β transgenic mice showed that

Table 3. Relationships between subtypes of dynamic skeletal muscle change and 1-year radiographic progression.

Subtypes of muscle change	Non-radiographic progression, *n* (%)	Radiographic progression, *n* (%)	OR (95% CI)	[a]AOR (95% CI)	[b]AOR (95% CI)
Baseline non-myopenia patients experiencing:					
an ASMI increase and non-myopenia at endpoint (subtype 1)	68 (82.9)	14 (17.1)	Ref	Ref	Ref
an ASMI decrease but also non-myopenia at endpoint (subtype 2)	59 (79.7)	15 (20.3)	1.235 (0.551–2.769)	1.289 (0.541–3.071)	1.287 (0.540–3.065)
an ASMI decrease to myopenia at endpoint (subtype 3)	8 (50.0)	8 (50.0)	**4.857 (1.559–15.132)**	**5.402 (1.491–19.576)**	**5.398 (1.492–19.535)**
Baseline myopenia patients experiencing:					
an ASMI increase to non-myopenia at endpoint (subtype 4)	17 (70.8)	7 (29.2)	2.000 (0.699–5.724)	2.584 (0.740–9.020)	2.570 (0.738–8.951)
an ASMI increase but also myopenia at endpoint (subtype 5)	32 (54.2)	27 (45.8)	**4.098 (1.897–8.853)**	**4.161 (1.207–14.342)**	**4.179 (1.211–14.415)**
an ASMI decrease and myopenia at endpoint (subtype 6)	32 (53.3)	28 (46.7)	**4.250 (1.974–9.151)**	**4.891 (1.668–14.345)**	**4.904 (1.671–14.395)**

ASMI increase, ΔASMI >0 from baseline to 12 months; ASMI decrease, ΔASMI ⩽0 from baseline to 12 months.
[a]AOR, adjusted odds ratio, adjusted for age, gender, smoking habits, BMI, BF%, disease duration, RF status, ACPA status, DAS28-CRP, HAQ-DI, mTSS, hypertension, type 2 diabetes and dyslipidemia at baseline and 1-year cumulative doses of medications including steroids, csDMARDs and biologic agents.
[b]AOR, adjusted odds ratio, adjusted for the same confounders in [a]AOR with substituting DAS28-ESR for DAS28-CRP.
Bolded numerals indicate data with statistical significance.
95% CI, 95% confidence interval; ACPA, anti-cyclic citrullinated peptide antibody; AOR, adjusted odds ratio; ASMI, appendicular skeletal muscle mass index; BF, body fat; BMI, body mass index; csDMARDs, ; DAS28-CRP, Disease Activity Score in 28 joints including C-reactive protein; DAS28-ESR, Disease Activity Score in 28 joints including erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, modified total Sharp score; OR, odds ratio; Ref, reference; RF, rheumatoid factor.

sustained over-expression of PGC1β promoted apoptosis and autophagy of myofibers by the regulation of mitochondrial biogenesis, and then caused a progressive decrease in muscle mass.[36] The cross-talk between muscle and bone may also be mediated through endocrine cytokines such as myostatin, irisin, and many others, although the relevance of this communication in RA has not been fully elucidated.[3]

Evidence-based clinical practice guidelines published in 2018 provide strong recommendations for resistance-based physical activity as the primary treatment for those with reduced skeletal muscle, especially sarcopenia.[37] A recent systematic review that guided the 2016 update of the EULAR recommendations for the management of early arthritis supports the beneficial effect of exercise programmes on pain and physical function.[38] The 2018 Physical Activity Guidelines for Americans also recommend general physical activity for adults.[27] However, a study of 5235 individuals with RA across 21 different countries found that the overwhelming majority (71%) did not participate in any regular physical activity, and only 14% exercised at least three times a week.[39] Endurance, aerobic and resistance training can improve body composition, including increasing lean mass and decreasing adiposity, improve physical function, and reduce cardiovascular risk in individuals with RA.[40–43] Whether muscle improvement therapy such as exercise can

reduce or block the progression of joint damage in RA is worth further exploration.

There are several limitations of our study. All patients were recruited at a single centre and treated with various medications. Compared with the Chinese Registry of Rheumatoid Arthritis, which depicted major cross-sectional data of Chinese RA patients ($n=8071$),[44] our study patients showed similar demographic characteristics except for a higher proportion of remission (37.8% *versus* 14.9%) at baseline. Although there was no significant difference in medications between RA patients with and without baseline myopenia, it would be necessary to carry out further multicenter studies with longer observational period and the same treatment regimen to remove this confounding effect. For the measurement of BC, BIA was used in this study rather than dual X-ray absorptiometry (DXA), which is considered as a gold standard. With comparable accuracy between BIA and DXA in Western or Asian populations, BIA has strengths, including non-radioactive, inexpensive, easy-manipulating and repeatable measures compared with DXA,[14,45,46] so BIA appeared well suited to assess dynamic skeletal muscle changes in this study. For muscle assessment, only skeletal muscle mass and subjective physical activity function were available in this study. Further measurements of muscle strength and objective physical performance to assess muscle function, and biological elements such as creatine phosphokinase and albumin levels would be needed in the future to investigate the link between muscle dysfunction and RA clinical outcomes.

In conclusion, reduced skeletal muscle at baseline both in active and remission RA, and even more, newly acquired myopenia at 1 year are independent prognostic risk factors of 1-year radiographic progression in RA. Patients with newly acquired myopenia at endpoint were the highest-risk individuals among six subtypes of dynamic skeletal muscle change. These data provide additional evidence of the effect of systemic inflammation on muscle, as well as on key organs like joint, and also imply some cross-talk between muscle and bone independent of systemic inflammation, which emphasizes the importance of dynamic monitoring of muscle mass during RA treatment. Further research on the underlying mechanism and the efficacy of muscle improvement therapy or even as a treatment target in RA management are worth exploration in future.

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Authors' contributions

LJZ, LY and MJD contributed equally to this work, including conceiving and designing the study, reading and analyzing documents, performing the statistical analysis and drafting the manuscript. Corresponding authors ZDH, LL and DL also conceived and participated in its design, advised on the search, read and analyzed documents, and edited the paper. MYQ, CCT and LQH participated in clinical assessment and BC measurement of RA patients, and critically revised the manuscript. CLF and YZH carried out the radiographic assessment and critically revised the manuscript. PM critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

Jian-Zi Lin, Yin Liu, Jian-Da Ma, Ying-Qian Mo, Chu-Tao Chen, Le-Feng Chen, Qian-Hua Li, Ze-Hong Yang, Dong-Hui Zheng, Li Ling, Pierre Miossec, Lie Dai declare that they have no competing interests.

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Ethics approval and consent to participate

This study was conducted in compliance with the Helsinki Declaration. The Medical Ethics Committee of Sun Yat-sen Memorial Hospital approved the protocol (SYSEC-2009-06 and SYSEC-KY-KS-012). All patients agreed to participate in this study and signed written informed consent.

Consent for publication

This study has obtained consent to publish from the participants (or legal parent or guardian for children) to report individual patient data. Details that might disclose the identity of the participants under study have been omitted.

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Data availability

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

Supplemental material

Supplemental material for this article is available online.

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