Ther Adv Chronic Dis
2020, Vol. 11: 1–18
DOI: 10.1177/2040622320975241

Neglected extra-articular manifestations in rheumatoid arthritis patients with normal body mass index: reduced skeletal muscle overlapping overfat

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Abstract

Background: Chronic inflammation in rheumatoid arthritis (RA) can induce reduced muscle mass (myopenia) and ectopic fat deposition probably showing normal body mass index (BMI). We aimed to investigate their body composition (BC) characteristics and clinical significance.

Methods: BMI and BC were collected in consecutive RA patients and control subjects. Myopenia was defined by appendicular skeletal muscle mass index (ASMI) $\leqslant$7.0 kg/m^2 in men and $\leqslant$5.7 kg/m^2 in women. Overfat was defined by body fat percentage (BF%) as $\geqslant$25% for men and $\geqslant$35% for women.

Results: There were 620 RA patients (57.6% with normal BMI) and 2537 control subjects (62.5% with normal BMI) recruited. After 1:1 age and sex matching with control subjects, RA patients with normal BMI (n = 240) showed significantly higher prevalence of myopenia (43.3% *versus* 22.1%) and overfat (19.2% *versus* 7.1%) as well as myopenia overlapping overfat (17.1% *versus* 3.3%). In all RA patients with normal BMI (n = 357), there were 18.2% patients with myopenia overlapping overfat who had the worst radiographic scores and highest rates of previous glucocorticoid treatment and hypertension. Compared with those without, normal BMI RA patients with previous glucocorticoid treatment (24.4% *versus* 10.3%) or hypertension (27.8% *versus* 13.6%) had a higher rate of myopenia overlapping overfat. Previous glucocorticoid treatment [odds ratio (OR) = 2.844, 95% confidence interval (CI) 1.441–5.614] and hypertension (OR = 2.452, 95% CI 1.283–4.685) were potential associated factors of myopenia overlapping overfat in RA patients with normal BMI.

Conclusion: Myopenia overlapping overfat is an important extra-articular manifestation which should not be ignored in RA patients with normal BMI, especially with glucocorticoid treatment and hypertension.

Keywords: body composition, body fat, body mass index, hypertension, rheumatoid arthritis, skeletal muscle

Received: 29 July 2020; revised manuscript accepted: 9 October 2020.

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Introduction

Rheumatoid arthritis (RA) is characterized by chronic systemic inflammation leading to irreversible erosive joint destruction and extra-articular manifestations such as vasculitis, cardiovascular events, interstitial lung disease, ocular disease, osteoporosis, and skeletal muscle depletion.[1,2] RA may predispose patients to frailty characterized by decrease of strength and endurance and reduced physiological function, which may enhance the individual's vulnerability for disability and/or death.[3] A recent study reported 28.8% RA patients with mild frailty, 15.5% with moderate frailty, and 19.6% with severe frailty.[4] Abnormal body composition (BC), especially reduced skeletal muscle mass, in RA patients has

been demonstrated in recent studies, which may be a potential condition predisposing to frailty. RA patients with reduced skeletal muscle mass may have serious consequences for their mortality, joint damage and physical dysfunction.[5,6] On the other hand, obesity as another kind of abnormal BC has also been investigated in RA patients for its increased risk of RA development, worse disease activity and more comorbidities such as hypertension, cardiovascular disease (CVD), and diabetes, but less joint destruction.[7–9]

Clinically, body weight or body mass index (BMI) is used to assess the nutritional status of individuals. Compared with underweight, overweight or obese individuals respectively, normal weight individuals are thought to be associated with the lowest mortality, as the ideal range for BMI in a general population.[10] However, BMI may fail to identify rheumatoid cachexia in RA patients, which is referred as loss of skeletal muscle mass and gain in fat mass causing stable weight; there is even no consensus for diagnosis criteria.[11] Chronic inflammation in RA can induce skeletal muscle atrophy and dysfunction as well as ectopic fat deposition.[2] This compensatory increased body fat may lead to normal weight or BMI in RA patients, and normal BMI was reported as high as 45–85% in Caucasian RA patients.[12,13] Therefore, detailed assessment of BC to distinguish muscle and fat mass as well as their distributions has critical importance in RA patients, especially those with normal weight or BMI. However, few studies have paid attention to these special subgroups of RA patients.

In this cross-sectional study, we compared BC characteristics between Chinese RA patients and matched control subjects with normal BMI, and explored their clinical significance.

Patients and methods

Study design and participants

This study was designed as a single-center cross-sectional study conducted in Chinese patients with RA at the Department of Rheumatology, Sun Yat-sen Memorial Hospital, Guangzhou, PR China, as described in our previous reports.[5] Consecutive RA patients aged ⩾16 years who fulfilled 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for RA[14] were recruited from August 2015 to June 2019. 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, or unable to stand stably and independently (e.g. stroke, severe spinal deformity, etc.). Control subjects were white-collar employees in Zhangjiang InnoPark of Shanghai voluntarily participating in this study from April 2015 to December 2016.[5] 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

Demographic and clinical data were collected at enrollment, including age, sex, disease duration, smoking habits, previous medications, comorbidities, disease activity, physical function, and radiographic indicators, as we described previously.[15,16] Clinical data included disease duration, 28-joint tender and swollen joint count (28TJC and 28SJC), patient and provider global assessment of disease activity (PtGA and PrGA; 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)], C-reactive protein (CRP; normal range 0–5 mg/L), rheumatoid factor (RF; normal range 0–20 mg/L, determined by nephelometry, Siemens Healthcare Diagnostics, Munich, Germany), and anti-cyclic citrullinated peptide antibody (ACPA, normal range 0–18 IU/mL, measured by enzyme-linked immunosorbent assay, Aesku Diagnostics, Wendelsheim, Germany). Disease activity was assessed with disease activity score in 28 joints with four variables including CRP (DAS28-CRP), simplified disease activity index (SDAI) and clinical disease activity index (CDAI). Disease activity defined by CDAI was divided into four categories: high disease activity (HDA, CDAI >22), moderate disease activity (MDA, $10<\text{CDAI}\leqslant 22$), low disease activity (LDA, $2.8<\text{CDAI}\leqslant 10$), and remission (CDAI $\leqslant 2.8$). Active RA was defined as CDAI >2.8.[17] The Chinese language version of Stanford Health Assessment Questionnaire disability index (HAQ-DI) was used to assess physical activity

function in eight categories (dressing, rising, eating, walking, hygiene, reaching, gripping, and activities).[18] Comorbidities included hypertension, type 2 diabetes, dyslipidemia, and CVD including both coronary artery disease (angina pectoris or myocardial infarction) and stroke (ischemic or hemorrhagic).[19]

Conventional radiographs of bilateral hands and wrists (anteroposterior view) of all RA patients were collected at enrollment. Radiographs were assessed according to the Sharp/van der Heijde modified score,[20] using the average scores of two experienced readers (ZHY from Radiology and LFC from Rheumatology) who were blinded to clinical data as we described previously.[15,16] Sixteen areas for joint erosion (JE) and 15 for joint space narrowing (JSN) of hands were assessed in each hand/wrist. The maximum score per single joint for JE is 5, and for JSN is 4, with the sum of JE (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 0.956.

BMI and body composition

BMI (kg/m^2) was calculated as weight (kg) divided height (m) squared. As recommended by the Working Group on Obesity in China,[21] subjects were categorized by BMI as underweight (BMI <18.5 kg/m^2), normal weight (18.5 kg/m$^2 \leqslant$ BMI <24 kg/m^2), overweight (24 kg/m$^2 \leqslant$ BMI <28 kg/m^2) and obese (BMI $\geqslant 28$ kg/m^2). BC was assessed by bioelectric impedance analysis (BIA) using an In Body 230 device (Biospace Co., Shanghai, China).[22] BC indicators included body fat percentage (BF%), the mass and distribution of muscle and fat in trunk and appendicular extremities. Appendicular skeletal muscle mass index (ASMI) was defined as appendicular skeletal muscle mass/height^2 (kg/m^2). Myopenia, referred as reduced skeletal muscle mass, 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.[5,23] Overfat was defined by BF% as $\geqslant 25\%$ for men and $\geqslant 35\%$ for women.[24] According to myopenia and overfat, subjects were divided into four BC subgroups: normal fat and non-myopenia (normal BC), myopenia but normal fat, overfat but non-myopenia, and myopenia overlapping overfat.

Exposure

Individuals with normal BMI were exposed to RA or not (control subjects).

Outcome

The primary outcome was myopenia overlapping overfat. The secondary outcomes were other BC characteristics including myopenia, overfat, and the other three BC subgroups.

Statistical analysis

IBM SPSS Statistics software for Windows version 25.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Values of continuous variables were presented as mean and standard deviation (SD) or median with interquartile range (IQR) according to distributions. Two independent samples *t*-test or the Mann–Whitney *U* test were used for comparison between two independent groups, and one-way analysis of variance or Kruskal–Wallis analysis of variance on ranks were used among three or more groups according to distributions. Categorical variables were presented as numbers and percentages. Chi-square test or Fisher's exact test were used to compare categorical variables. Bonferroni correction was used for multiple comparisons in three or more groups.

Propensity score matching was used to balance age and sex distribution between two groups with or without exposure (RA patients *versus* control subjects in 1:1 matching). Conditional logistic regression analysis was used to compare continuous and categorical variables between matched two groups in all and sex stratification. Further analysis of disease characteristics in RA patients with normal BMI was performed. To validate our findings, stratified analyses were performed for previous glucocorticoid treatment or hypertension in RA patients with normal BMI. Univariate and multivariate logistic regression analyses by calculating odds ratio (OR) and 95% confidence interval (CI) were used to identify potential associated factors of overlapping myopenia and overfat in normal BMI RA patients. Stepwise multivariate logistic regression followed the rule that variables were included when the p value was <0.05 or removed when the p value was >0.10. Potential confounders were adjusted including age, sex, smoking habits and CDAI. All significance tests were two-tailed and were conducted at the 5% significance level.

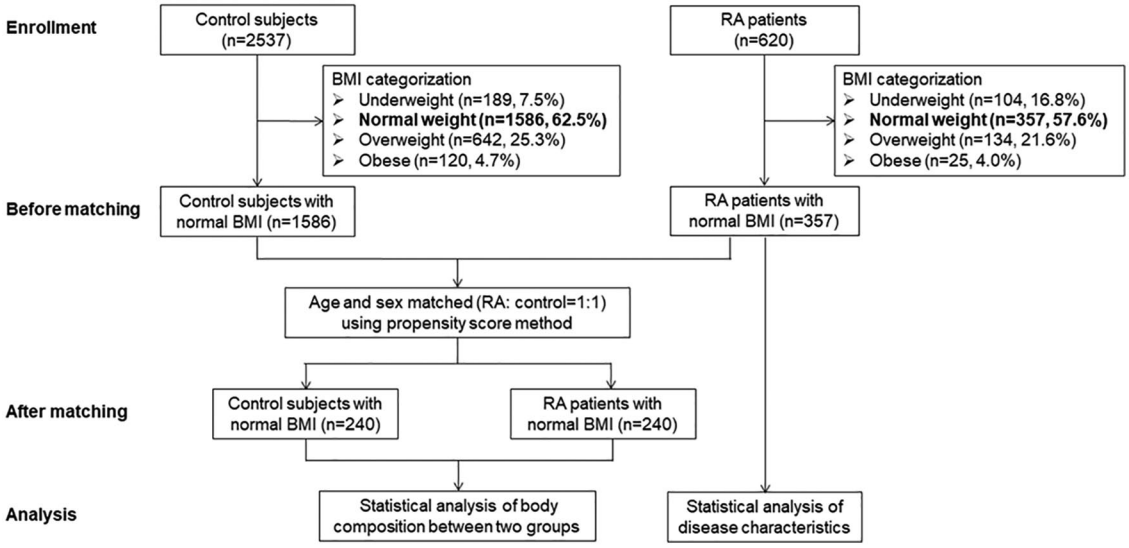

Figure 1. Flow diagram of matched rheumatoid arthritis (RA) patients and control subjects with normal body mass index (BMI) for statistical analysis.

Results

Baseline characteristics of all RA patients

There were 620 RA patients and 2537 control subjects recruited. The baseline characteristics of RA patients are shown in Table 1. In the RA group, the mean age was 49.5 ± 12.8 years with 82.3% female. The median disease duration was 48 months (IQR 23–108), 4.7% with short disease duration (<6 months), and 69.4% with long disease duration (>24 months). According to CDAI, there were 20.5% RA patients with HDA, 28.1% MDA, 28.7% LDA, and 22.7% in remission. There were 17.3% patients without previous glucocorticoid or disease modifying anti-rheumatic drugs (DMARDs) therapy for 6 months before enrollment (treatment naïve). There were 208 (33.5%) RA patients with hypertension, 53 (8.5%) with type 2 diabetes, 66 (10.6%) with dyslipidemia and 32 (5.2%) with CVD. In the control group, the mean age was 33.6 ± 9.6 years with 52.8% female. Compared with control subjects, RA patients were older (49.5 ± 12.8 years *versus* 33.6 ± 9.6 years, $p < 0.001$) with a predominance of females (82.3% *versus* 52.8%, $p < 0.001$).

Comparisons of BC characteristics between matched RA patients and control subjects with normal BMI

In all RA patients, 104 (16.8%) were underweight, 357 (57.6%) were normal weight, 134 (21.6%) were overweight, and 25 (4.0%) were obese, while there were 189 (7.5%) underweight, 1586 (62.5%) normal weight, 642 (25.3%) overweight, and 120 (4.7%) obese in control subjects. Compared with control subjects with normal BMI, RA patients with normal BMI were older (49.3 ± 12.3 years *versus* 32.3 ± 8.8 years, $p < 0.001$) with a predominance of females (84.9% *versus* 61.7%, $p < 0.001$).

In order to balance the effects of age and sex on BC characteristics between two groups, RA patients with normal BMI were matched with age and sex 1:1 to control subjects with normal BMI in propensity score method (Figure 1). After matching, there were 240 RA patients and 240 control subjects included, with no difference in age, sex and BMI (Supplemental material Table 1 online). Compared with the control group, matched RA patients with normal BMI had significantly higher rate of myopenia (43.3% *versus* 22.1%) with lower ASMI (5.9 ± 0.8 kg/m^2 *versus* 6.3 ± 0.8 kg/m^2), higher rate of overfat (19.2% *versus* 7.1%) with higher BF% (29.3 ± 6.4% *versus* 26.7 ± 6.3%), and higher prevalence of abnormal BC (45.4% *versus* 25.8%), including higher proportion of myopenia but normal fat subgroup (26.2% *versus* 18.7%) and myopenia overlapping overfat subgroup (17.1% *versus* 3.3%, $p < 0.001$; Figure 2), with all lower muscle indicators and higher fat indicators distributed in trunk and appendicular

Table 1. Baseline characteristics of RA patients.

Characteristics	RA patients ($n = 620$)
Age, years, mean ± SD	49.5 ± 12.8
Female, *n* (%)	510 (82.3)
Active smoking, *n* (%)	93 (15.0)
Disease duration, months, median (IQR)	48 (23–108)
Positive RF, *n* (%)	402 (64.8)
Positive ACPA, *n* (%)	432 (69.7)
Core disease activity indicators	
28TJC, median (IQR)	2 (0–6)
28SJC, median (IQR)	1 (0–4)
PtGA, cm, median (IQR)	3 (1–5)
PrGA, cm, median (IQR)	3 (1–5)
Pain VAS, cm, median (IQR)	2 (2–4)
ESR, mm/h, median (IQR)	27 (15–49)
CRP, mg/L, median (IQR)	4.1 (3.3–15.1)
DAS28-CRP, median (IQR)	3.2 (2.0–4.4)
SDAI, median (IQR)	11.2 (4.3–21.7)
CDAI, median (IQR)	10 (4–20)
Functional indicator	
HAQ-DI, median (IQR)	0.13 (0.00–0.72)
Radiographic indicators	
mTSS, median (IQR)	11 (4–33)
JSN subscore, median (IQR)	3 (0–12)
JE subscore, median (IQR)	8 (3–21)
Previous medications	
Treatment naïve, *n* (%)	107 (17.3)
Glucocorticoid, *n* (%)	341 (55.0)
Methotrexate, *n* (%)	409 (66.0)
Leflunomide, *n* (%)	324 (52.3)
Hydroxychloroquine, *n* (%)	114 (18.4)
Sulfasalazine, *n* (%)	50 (8.1)
Cyclosporin A, *n* (%)	40 (6.5)
Biologic agents, *n* (%)	38 (6.1)
Comorbidities	
Hypertension, *n* (%)	208 (33.5)
Type 2 diabetes, *n* (%)	53 (8.5)
Dyslipidemia, *n* (%)	66 (10.6)
CVD, *n* (%)	32 (5.2)

28SJC, 28-swollen joint count; 28TJC, 28-joint tender count; ACPA, anti-cyclic citrullinated peptide antibody; CDAI, clinical disease activity index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28-CRP, disease activity score in 28 joints with four variables including CRP; ESR, erythrocyte sedimentation rate; HAQ-DI, Stanford Health Assessment Questionnaire disability index; IQR, interquartile range; JE, joint erosion; JSN, joint space narrowing; mTSS, modified total Sharp score; Pain VAS, pain visual analogue scale; 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.

extremities (Supplemental material Table 1 online).

In further comparisons by sex stratification, there were 208 (86.7%) female and 32 (13.3%) male included in matched RA patients and control subjects with normal BMI respectively (Supplemental Table 1). Compared with female control subjects, matched female RA patients with normal BMI had a significantly higher rate of myopenia (45.2% *versus* 24.0%) with lower ASMI ($5.7 \pm 0.6\,kg/m^2$ *versus* $6.0 \pm 0.5\,kg/m^2$), higher rate of overfat (19.2% *versus* 6.7%) with higher BF% ($30.8 \pm 4.9\%$ *versus* $28.1 \pm 5.1\%$, all $p < 0.01$), and higher prevalence of abnormal BC (47.1% *versus* 27.5%), including higher proportion of myopenia but normal fat subgroup (27.9% *versus* 20.7%) and myopenia overlapping overfat subgroup (17.3% *versus* 3.4%, $p < 0.001$; Figure 2). Compared with male control subjects, matched male RA patients with normal BMI had significantly lower ASMI ($7.2 \pm 0.7\,kg/m^2$ *versus* $7.7 \pm 1.1\,kg/m^2$), while there were no differences in the rates of myopenia, overfat or abnormal BC subgroups.

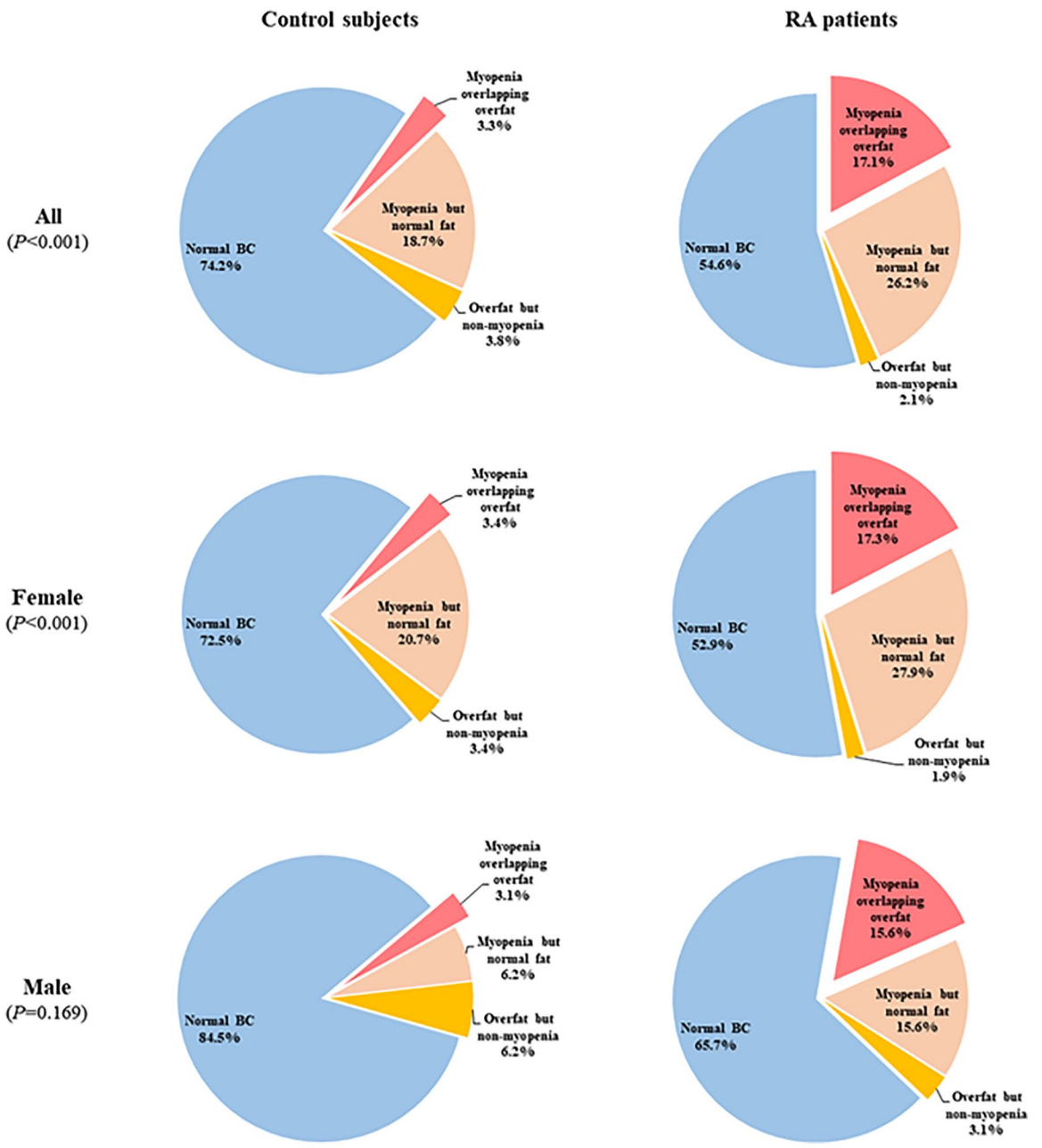

Figure 2. Comparisons of body composition (BC) subgroups between matched rheumatoid arthritis (RA) patients and control subjects with normal body mass index.
All, $N = 240$; female, $n = 208$; male, $n = 32$.

Comparisons of disease characteristics among BC subgroups of RA patients with normal BMI

In all RA patients with normal BMI ($n = 357$), there were 187 (52.4%) with normal BC, 99 (27.7%) with myopenia but normal fat, six (1.7%) with overfat but non-myopenia, and 65 (18.2%) with myopenia overlapping overfat. Because of the small number in the overfat but non-myopenia subgroup, statistical analysis of disease characteristics was performed in the other three subgroups (Table 2). There were significant differences in age, disease duration, almost all core disease activity indicators, functional indicator, radiographic assessment indicators, and the rates of previous glucocorticoid treatment and hypertension among the three subgroups. RA patients with myopenia overlapping overfat had the highest mTSS (median 24 *versus* 16 *versus* 7),

Table 2. Comparisons of disease characteristics among BC subgroups in rheumatoid arthritis patients with normal BMI.

Characteristics	All patients with normal BMI *n* = 357	Normal BC *n* = 187	Myopenia but normal fat *n* = 99	Myopenia overlapping overfat *n* = 65	*p*[a]
Age, years, mean ± SD	49.3 ± 12.3	51.5 ± 7.5	47.7 ± 11.5	53.5 ± 12.1	**0.040**
Female, *n* (%)	303 (84.9)	154 (82.4)	87 (87.9)	57 (84.9)	0.565
Active smoking, *n* (%)	48 (13.4)	28 (15.0)	11 (11.1)	8 (12.3)	0.810
Disease duration, months, median (IQR)	58 (24–118)	40 (18–96)	72 (24–108)	96 (36–156)[b]	**<0.001**
Core disease activity indicators					
28TJC, median (IQR)	2 (0–5)	2 (0–4)	3 (1–7)	2 (0–8)	**0.031**
28SJC, median (IQR)	1 (0–4)	1 (0–4)	2 (0–6)[b]	2 (0–6)	**0.019**
PtGA, cm, median (IQR)	3 (1–5)	2 (0–5)	3 (1–6)	**5 (2–6)**[b]	**0.002**
PrGA, cm, median (IQR)	3 (1–5)	2 (0–5)	3 (1–5)	**5 (2–6)**[b]	**<0.001**
Pain VAS, cm, median (IQR)	2 (2–4)	2 (1–4)	2 (2–4)	**4 (2–5)**[b]	**0.018**
ESR, mm/h, median (IQR)	29 (15–50)	26 (15–42)	31 (16–53)	**32 (20–73)**[b]	**0.022**
CRP, mg/L, median (IQR)	3.9 (3.3–15.4)	3.3 (3.3–8.8)	5.6 (3.3–23.7)	**8.4 (3.3–32.2)**[b]	**<0.001**
DAS28-CRP, median (IQR)	3.2 (2.0–4.5)	3.0 (1.8–3.9)	3.4 (2.2–4.7)	**3.8 (2.4–5.1)**[b]	**0.002**
SDAI, median (IQR)	11.3 (4.3–22.1)	9.1 (3.0–18.3)	11.3 (5.0–24.4)	**16.2 (5.8–29.2)**[b]	**0.001**
CDAI, median (IQR)	10 (4–20)	8 (2–16)	11 (4–22)	**14 (5–26)**[b]	**0.004**
Functional indicator					
HAQ-DI, median (IQR)	0.25 (0.00–0.75)	0.12 (0.00–0.50)	**0.25 (0.00–0.75)**[b]	**0.63 (0.06–1.25)**[b]	**<0.001**
Radiographic assessment					
mTSS, median (IQR)	11 (3–31)	7 (2–21)	**16 (4–39)**[b]	**24 (10–115)**[b,c]	**<0.001**
JSN subscore, median (IQR)	3 (0–12)	1 (0–6)	**5 (0–16)**[b]	**11 (2–47)**[b,c]	**<0.001**

(Continued)

Table 2. (Continued)

Characteristics	All patients with normal BMI $n=357$	Normal BC $n=187$	Myopenia but normal fat $n=99$	Myopenia overlapping overfat $n=65$	p^a
JE subscore, median (IQR)	8 (2–20)	5 (2–13)	**10 (3–22)**[b]	**14 (7–64)**[b,c]	**<0.001**
Previous medications					
Treatment naïve, *n* (%)	63 (17.6)	34 (18.2)	21 (21.2)	7 (10.8)	0.388
Glucocorticoid, *n* (%)	201 (56.3)	98 (52.4)	49 (49.5)	**49 (75.4)**[b,c]	**0.002**
Methotrexate, *n* (%)	235 (65.8)	122 (65.2)	63 (63.6)	44 (67.7)	0.327
Leflunomide, *n* (%)	187 (52.4)	106 (56.7)	44 (44.4)	33 (50.8)	0.217
Hydroxychloroquine, *n* (%)	70 (19.6)	35 (18.7)	23 (23.2)	9 (13.8)	0.122
Sulfasalazine, *n* (%)	25 (7.0)	14 (7.5)	7 (7.1)	4 (6.2)	0.898
Cyclosporin A, *n* (%)	21 (5.9)	8 (4.3)	9 (9.1)	4 (6.2)	0.377
Biologic agents, *n* (%)	16 (4.5)	10 (5.3)	6 (6.1)	0 (0)	0.237
Comorbidities					
Hypertension, *n* (%)	115 (32.2)	53 (28.3)	28 (28.3)	**32 (49.2)**[b,c]	**0.014**
Type 2 diabetes, *n* (%)	23 (6.4)	12 (6.4)	5 (5.1)	6 (9.2)	0.596
Dyslipidemia, *n* (%)	33 (9.2)	18 (9.6)	7 (7.1)	8 (12.3)	0.587
CVD, *n* (%)	16 (4.5)	7 (3.7)	5 (5.1)	4 (6.2)	0.797

Overfat but non-myopenia subgroup ($n=6$) was not included in statistical analysis.
[a]Comparison in three groups by Kruskal–Wallis test.
[b]Compared with normal body composition patients in Bonferroni correction, $p<0.0167$.
[c]Compared with myopenia but normal fat patients in Bonferroni correction, $p<0.0167$.
28SJC, 28-swollen joint count; 28TJC, 28-joint tender count; BC, body composition; BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28-CRP, disease activity score in 28 joints with four variables including CRP; ESR, erythrocyte sedimentation rate; HAQ-DI, Stanford Health Assessment Questionnaire disability index; JE, joint erosion; JSN, joint space narrowing; mTSS, modified total Sharp score; Pain VAS, pain visual analogue scale; PrGA, provider global assessment of disease activity; PtGA, patient global assessment of disease activity; SDAI, simplified disease activity index.
BC, body composition; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

subscores of JSN (median 11 *versus* 5 *versus* 1) and JE (median 14 *versus* 10 *versus* 5), and highest rates of previous glucocorticoid treatment (75.4% *versus* 49.5% *versus* 52.4%) and hypertension (49.2% *versus* 28.3% *versus* 28.3%) in comparison with the other two subgroups respectively. Additionally, they also had significantly longer disease duration (median 96 months *versus* 40 months), higher core disease activity indicators including PtGA (median 5 cm *versus* 2 cm), PrGA (median 5 cm *versus* 2 cm), Pain VAS (median 4 cm *versus* 2 cm), ESR (median 32 mm/h *versus* 26 mm/h), CRP (median 8.4 mg/L *versus* 3.3 mg/L), DAS28-CRP (median 3.8 *versus* 3.0), SDAI (median 16.2 *versus* 9.1), CDAI (median 14 *versus* 8), and higher HAQ-DI (median 0.63 *versus* 0.12) when compared with the normal BC subgroup (all $p < 0.0167$, Bonferroni correction; Table 2).

Clinical features of normal BMI RA patients with previous glucocorticoid treatment or hypertension

In all RA patients with normal BMI, there were 201 (56.3%) with previous glucocorticoid treatment and 115 (32.2%) with hypertension. Compared with those without previous glucocorticoid treatment, normal BMI RA patients with previous glucocorticoid treatment had higher radiographic assessment indicators including mTSS (median 12 *versus* 9) and JE subscore (median 10 *versus* 6), higher rate of overfat (26.9% *versus* 10.9%) with higher BF% ($30.1 \pm 7.0\%$ *versus* $28.1 \pm 6.2\%$, all $p < 0.05$; Table 3), and higher prevalence of abnormal BC (51.3% *versus* 43.0%), especially a higher proportion of myopenia overlapping overfat subgroup (24.4% *versus* 10.3%, $p = 0.002$; Figure 3).

Compared with those without hypertension, normal BMI RA patients with hypertension were older (55.0 ± 10.4 years *versus* 46.5 ± 12.2 years) with higher PtGA (median 4 cm *versus* 3 cm), higher PrGA [median (IQR): 3 (1–6) cm *versus* 3 (1–5) cm], higher HAQ-DI (0.25 *versus* 0.13), higher BMI (21.6 ± 1.5 kg/m^2 *versus* 21.1 ± 1.5 kg/m^2), higher rate of overfat (29.6% *versus* 15.3%, all $p < 0.05$, Table 3), and higher prevalence of abnormal BC (53.9% *versus* 44.6%) especially higher proportion of myopenia overlapping overfat subgroup (27.8% *versus* 13.6%, $p = 0.014$, Figure 3)

Associated factors of myopenia overlapping overfat in RA patients with normal BMI

To explore the potential associated factors of myopenia overlapping overfat in RA patients with normal BMI, univariate and multivariate logistic regression analyses were performed (Figure 4). Univariate logistic regression analysis showed that myopenia overlapping overfat was positively associated with age (OR = 1.038, 95% CI 1.013–1.063), disease duration (OR = 1.007, 95% CI 1.003–1.010), positive RF (OR = 2.213, 95% CI 1.151–4.252), all core disease activity indicators, HAQ-DI (OR = 2.213, 95% CI 1.526–3.210), radiographic assessment indicators, previous glucocorticoid treatment (OR = 2.821, 95% CI 1.534–5.188) and hypertension (OR = 2.442, 95% CI 1.411–4.227; Figure 4A).

Further stepwise multivariate logistic regression analysis showed that CRP (OR = 1.017, 95% CI 1.004–1.030), mTSS (OR = 1.016, 95% CI 1.010–1.023), previous glucocorticoid treatment (OR = 2.823, 95% CI 1.438–5.544), and hypertension (OR = 2.753, 95% CI 1.490–5.087; Figure 4B) were potential associated factors of myopenia overlapping overfat. After adjustment for potential confounders including age, sex, smoking habits, and CDAI, multivariate logistic regression analysis confirmed that CRP (OR = 1.017, 95% CI 1.002–1.032), mTSS (OR = 1.016, 95% CI 1.009–1.023), previous glucocorticoid treatment (OR = 2.844, 95% CI 1.441–5.614), and hypertension (OR = 2.452, 95% CI 1.283–4.685; Figure 4C) were still associated with myopenia overlapping overfat in RA patients with normal BMI.

Discussion

This is the first study to compare BC characteristics in RA patients with normal BMI with matched controls, which showed higher prevalence of myopenia overlapping overfat (17.1% *versus* 3.3%) and those normal BMI RA patients with myopenia overlapping overfat had the worst radiographic scores as well as the highest rates of previous glucocorticoid treatment and hypertension. There were 24.4% and 27.8% with myopenia overlapping overfat in normal BMI RA patients with previous glucocorticoid treatment and hypertension respectively. Previous glucocorticoid treatment (OR of 2.844-fold) and hypertension (OR of 2.452-fold) were their potential associated factors. All these findings indicate that myopenia

Table 3. Comparisons of clinical and BC characteristics between normal BMI rheumatoid arthritis patients with and without previous glucocorticoid or hypertension.

Characteristics	Previous glucocorticoid			Hypertension		
	Without *n* = 156	With *n* = 201	*p*	Without *n* = 242	With *n* = 115	*p*
Age, years, mean ± SD	48.8 ± 12.6	49.6 ± 12.1	0.551	46.5 ± 12.2	55.0 ± 10.4	**<0.001**
Female, *n* (%)	134 (85.9)	169 (84.1)	0.658	209 (86.4)	94 (81.7)	0.254
Active smoking, *n* (%)	21 (13.5)	27 (13.4)	0.994	31 (12.8)	17 (14.8)	0.610
Disease duration, months, median (IQR)	48 (24–120)	60 (22–115)	0.785	60 (24–111)	48 (20–120)	0.973
Positive RF, *n* (%)	100 (64.1)	140 (69.7)	0.268	164 (67.8)	76 (66.1)	0.752
Positive ACPA, *n* (%)	118 (75.6)	141 (70.1)	0.249	182 (75.2)	77 (67.0)	0.103
Core disease activity indicators						
28TJC, median (IQR)	2 (0–7)	2 (0–5)	0.919	2 (0–5)	2 (0–7)	0.360
28SJC, median (IQR)	1 (0–4)	1 (0–4)	0.808	1 (0–4)	1 (0–4)	0.966
PtGA, cm, median (IQR)	3 (0–5)	3 (1–6)	0.391	3 (1–5)	4 (1–6)	**0.040**
PrGA, cm, median (IQR)	3 (0–5)	3 (1–5)	0.451	3 (1–5)	3 (1–6)	**0.030**
Pain VAS, cm, median (IQR)	2 (1–4)	2 (2–4)	0.745	2 (2–4)	3 (2–4)	0.119
ESR, mm/h, median (IQR)	33 (16–52)	27 (15–49)	0.224	26 (16–47)	33 (15–68)	0.104
CRP, mg/L, median (IQR)	3.5 (3.3–15.7)	4.2 (3.3–15.5)	0.899	3.4 (3.3–13.0)	4.8 (3.3–21.6)	0.182
DAS28-CRP, median (IQR)	3.3 (1.8–4.6)	3.1 (2.2–4.5)	0.685	3.2 (2.0–4.2)	3.3 (2.0–4.9)	0.179
SDAI, median (IQR)	11.4 (2.3–22.2)	10.7 (4.5–21.9)	0.802	10.3 (3.3–20.9)	12.3 (4.3–25.9)	0.118
CDAI, median (IQR)	11 (2–21)	10 (4–19)	0.774	10 (3–18)	12 (4–23)	0.144

(Continued)

Table 3. (Continued)

Characteristics	Previous glucocorticoid			Hypertension		
	Without *n* = 156	With *n* = 201	*p*	Without *n* = 242	With *n* = 115	*p*
Functional indicator						
HAQ-DI, median (IQR)	0.13 (0.00–0.75)	0.25 (0.00–0.63)	0.874	0.13 (0.00–0.63)	0.25 (0.00–0.88)	**0.037**
Radiographic assessment						
mTSS, median (IQR)	9 (2–25)	12 (4–42)	**0.018**	11 (3–31)	11 (3–32)	0.877
JSN subscore, median (IQR)	2 (0–10)	3 (0–16)	0.083	3 (0–11)	2 (0–13)	0.734
JE subscore, median (IQR)	6 (2–15)	10 (3–25)	**0.004**	7 (2–20)	8 (2–18)	0.810
BMI and BC						
BMI, kg/m^2, mean ± SD	21.2 ± 1.5	21.3 ± 1.5	0.384	21.1 ± 1.5	21.6 ± 1.5	**0.008**
ASMI, kg/m^2, mean ± SD	6.0 ± 0.8	5.8 ± 0.9	0.085	5.9 ± 0.8	5.8 ± 0.9	0.321
Myopenia, *n* (%)	66 (42.3)	98 (48.8)	0.225	104 (43.0)	60 (52.2)	0.103
BF%, mean ± SD	28.1 ± 6.2	30.1 ± 7.0	**0.005**	29.0 ± 6.4	29.7 ± 7.3	0.354
Overfat, *n* (%)	17 (10.9)	54 (26.9)	**<0.001**	37 (15.3)	34 (29.6)	**0.002**

28SJC, 28-swollen joint count; 28TJC, 28-joint tender count; ACPA, anti-cyclic citrullinated peptide antibody; ASMI, appendicular skeletal muscle mass index; BC, body composition; BF%, body fat percentage; BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28-CRP, disease activity score in 28 joints with four variables including CRP; ESR, erythrocyte sedimentation rate; HAQ-DI, Stanford Health Assessment Questionnaire disability index; IQR, interquartile range; JE, joint erosion; JSN, joint space narrowing; mTSS, modified total Sharp score; Pain VAS, pain visual analogue scale; PrGA, provider global assessment of disease activity; PtGA, patient global assessment of disease activity; RF, rheumatoid factor; SD, standard deviation; SDAI, simplified disease activity index.

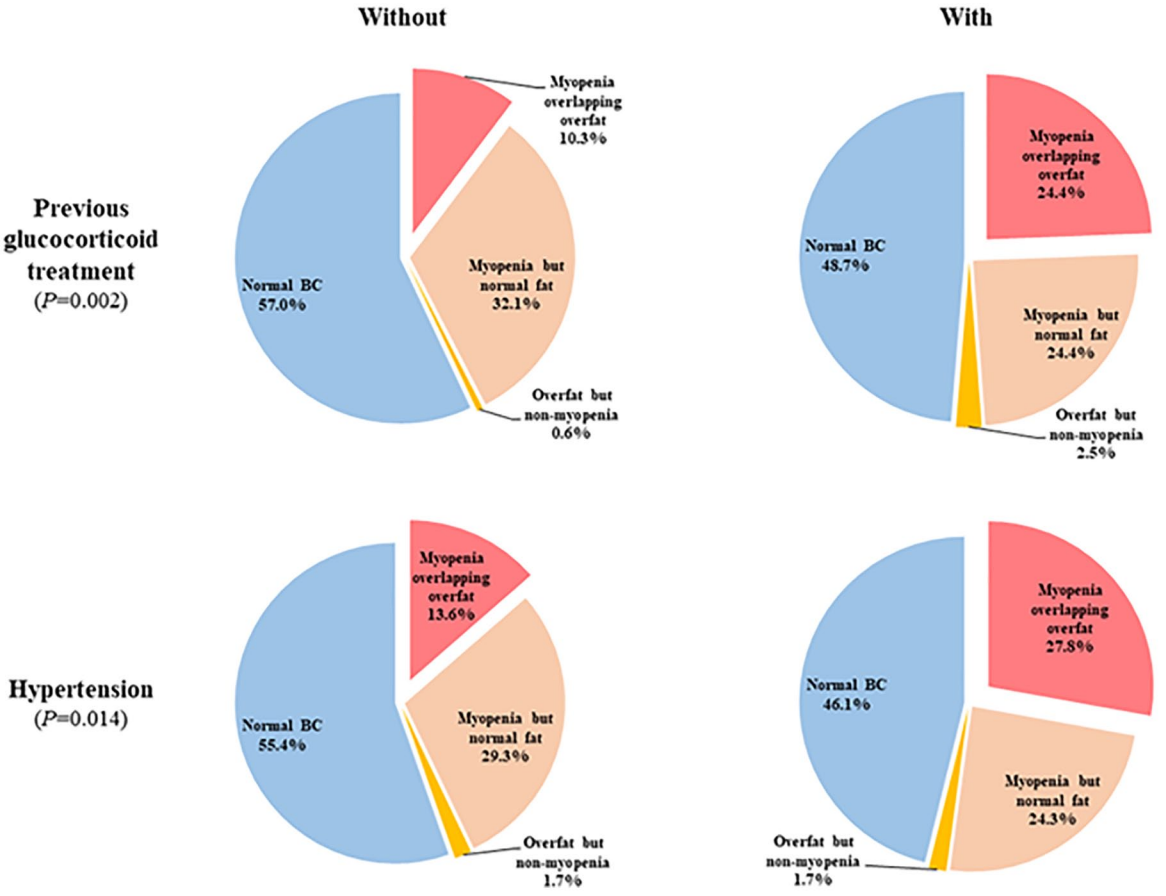

Figure 3. Comparisons of body composition (BC) subgroups between normal body mass index rheumatoid arthritis patients with and without previous glucocorticoid treatment or hypertension. Without previous glucocorticoid treatment, $n = 156$; with previous glucocorticoid treatment, $n = 201$; without hypertension, $n = 314$; with hypertension, $n = 43$.

overlapping overfat is an important extra-articular manifestation which should not be ignored in RA patients even with normal BMI, especially those with glucocorticoid treatment and hypertension.

Recently, the coexistence of reduced skeletal muscle and increased fat has raised attention. Sarcopenic obesity has been proposed to identify obesity with low skeletal muscle mass and function, which is largely limited to the aging population, with different definitions, BC assessment techniques, and obesity markers.[25] A cross-national analysis of 18,363 elderly people from Finland, Poland, Spain, China, Ghana, India, Mexico, Russia, and South Africa reported that the prevalence of sarcopenic obesity was 4.7% in the overall population with a range from 1.3% (India) to 11.0% (Spain).[26] Similarly, for RA patients, rheumatoid cachexia was proposed by Engvall *et al.*[27] and Elkan *et al.*[28] with different cut-off points of low fat free mass index and high fat mass index of Swedish healthy adult population, and its prevalence ranges from 15% to 32% under different criteria in a recent meta-analysis.[29] However, the coexistence of reduced skeletal muscle and increased fat in normal BMI in the general population and RA patients is rarely studied. Due to "sarcopenic obesity" mainly for the elderly, and lack of consensus for the diagnosis of both "sarcopenic obesity" and "rheumatoid cachexia", "myopenia overlapping overfat" was adopted in our study. Our data showed an approximate rate of myopenia overlapping overfat in normal BMI control subjects (3.3%) compared with sarcopenic obesity in a Chinese population (2.9%).[26] We first reported the high prevalence of myopenia overlapping overfat in normal BMI RA patients (17.3% for

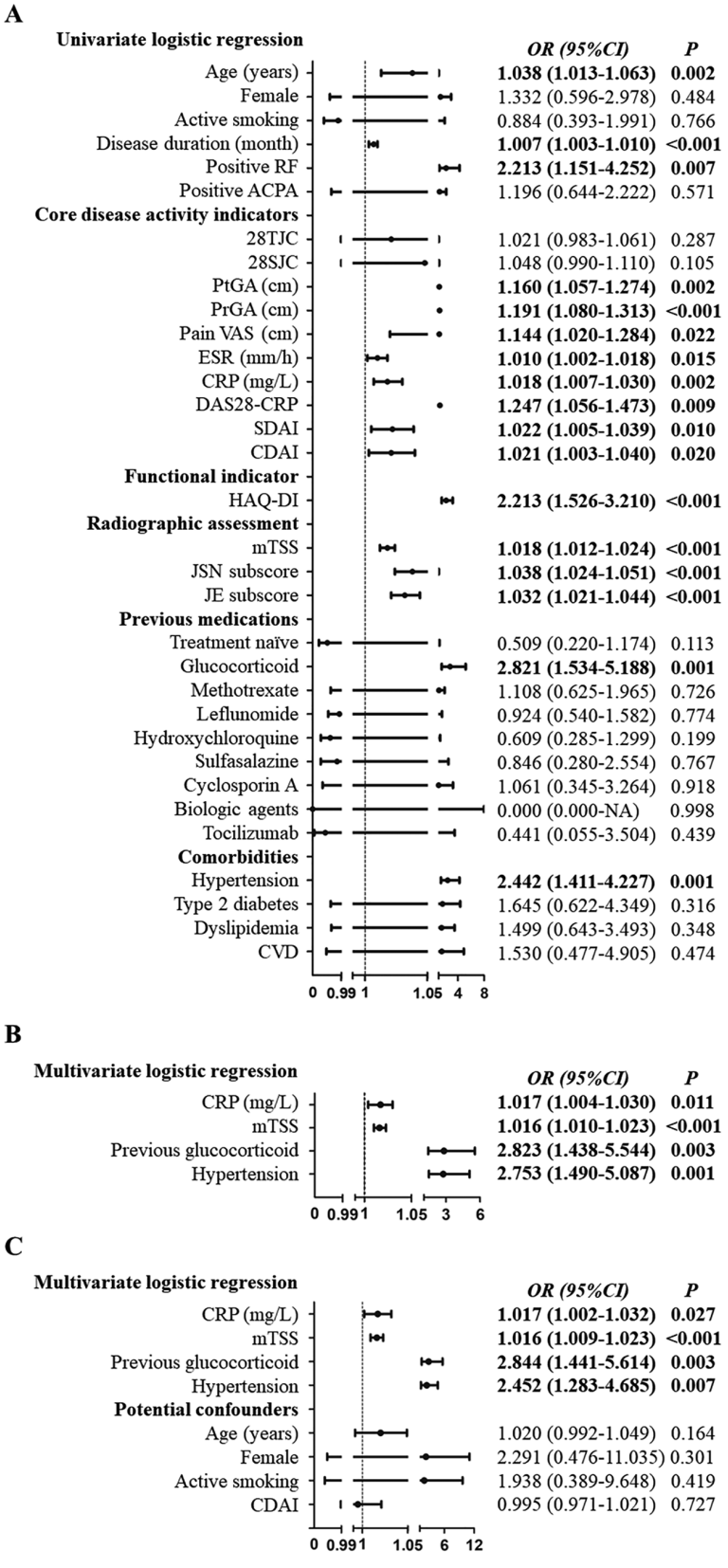

Figure 4. *(Continued)*

Figure 4. Logistic regression analysis for potential associated factors of myopenia overlapping overfat in rheumatoid arthritis patients with normal body mass index.
28SJC, 28-swollen joint count; 28TJC, 28-joint tender count; ACPA, anti-cyclic citrullinated peptide antibody; CDAI, clinical disease activity index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28-CRP, disease activity score in 28 joints with four variables including CRP; ESR, erythrocyte sedimentation rate; HAQ-DI, Stanford Health Assessment Questionnaire disability index; JE, joint erosion; JSN, joint space narrowing; mTSS, modified total Sharp score; OR, odds ratio in logistic regression; Pain VAS, pain visual analogue scale; PrGA, provider global assessment of disease activity; PtGA, patient global assessment of disease activity; RF, rheumatoid factor; SDAI, simplified disease activity index.

female and 15.6% for male), especially those with previous glucocorticoid treatment (24.4%) and hypertension (27.8%). All these rates were higher than that in all RA patients (14.0%) in our previous study,[5] which indicates myopenia overlapping overfat is common in RA patients even with normal BMI.

Several factors can affect both muscle and fat simultaneously in RA. Overexpression of pro-inflammatory cytokines in RA can stimulate proteasome-dependent proteolysis, causing muscle atrophy,[2,30] and induce ectopic fat accumulation in muscle by reduced β-oxidation of fatty acid and upregulated fatty acid uptake.[31] Apart from inflammation, varying degrees of pain, limited joint mobility, and lack of physical activity are thought to be contributing factors to muscle loss and fat deposits in RA.[32] Previous studies showed that Swedish RA patients with rheumatoid cachexia were associated with serum CRP levels, DAS28, HAQ score, cholesterol levels and high frequency of hypertension.[27,28] Another Mexico study showed that rheumatoid cachexia was related to disability (OR of 4.69) but negatively related to methotrexate treatment (OR of 0.19),[33] while a review reported no association between rheumatoid cachexia and rheumatoid disease severity, such as disease duration, swollen joint counts, mean ESR, or prednisolone treatment.[13] The clinical features in normal BMI RA patients with myopenia overlapping overfat have not been reported. Our study first showed that normal BMI RA patients with myopenia overlapping overfat had the worst radiographic scores as well as the highest rates of previous glucocorticoid treatment and hypertension. CRP, mTSS, previous glucocorticoid treatment, and hypertension are their potential associated factors, which is worth exploring in the future.

Abnormal BC in RA has strong associations not only with chronic inflammation but also with pharmacotherapies, especially glucocorticoids.[34] Extended exposure to glucocorticoids can cause Cushing's syndrome,[35] while early RA patients treated with high-dose, step-down prednisolone regimen reported increased fat mass but no fat redistribution from peripheral to central tissues.[36] Glucocorticoids do play an important role in regulating muscle and fat metabolism; however, in RA patients, the net effect of the disease itself and glucocorticoid treatment on BC remains to be determined.[35] Glucocorticoids can break down skeletal muscle by inhibiting its regeneration by attenuating myogenic cell proliferation and differentiation.[37] Meanwhile, glucocorticoids have potent effects on improvement of muscle repair and function by inflammation reduction.[38] Recent studies reported that physiological levels of glucocorticoids may increase muscle mass and muscle strength, especially at a younger age,[39] and enhance physical performance in athletes.[40] In addition, different effects of glucocorticoids are also shown on fat metabolism. Long-term glucocorticoid treatment results in enhancement of lipogenesis, increased visceral obesity, and hypertension, while acute glucocorticoid exposure typically promotes lipolysis and weight loss.[41] Our cross-sectional data underline that glucocorticoid treatment is not only associated with worse radiographic scores, but also has a high risk of 2.7-fold for myopenia overlapping overfat even in those with normal BMI who are considered as without Cushing's syndrome. Besides glucocorticoid, other medications such as non-steroidal anti-inflammatory drugs, hydroxychloroquine, and tumor necrosis factor-α inhibitors are reported to possibly contribute to a lesser extent to skeletal muscle, while interleukin (IL)-6/Janus kinase/signal transducer activator of transcription (JAK-STAT) inhibition has beneficial effects on improving muscle mass and lipid profiles.[34] But our logistic regression analysis showed no association between previous anti-IL-6 treatment and myopenia overlapping overfat, which may due to a small sample of patients with previous tocilizumab treatment. Although 2019 EULAR recommends that short-term glucocorticoids should

be tapered as rapidly as clinically feasible in RA management,[42] IL-6/JAK-STAT inhibition rather than glucocorticoid, taking the above into account, may be preferred for early RA treatment, even in those with normal BMI.

Recent reports from the Australian Rheumatology Association Database and Asian studies showed that RA patients had high prevalence of comorbidities, including hypertension (31.3–35.2%), diabetes (8.4–10.2%), dyslipidemia (18.4%), ischemic heart disease (5.1–6.8%), and cardiovascular accident (3.6%).[43,44] In particular, prevalence of hypertension ranges from 4% to 73% in RA patients.[45] With the development of novel treatments, especially biologic agents, RA no longer represents a direct threat to life; instead CVD mortality is increased by ~50% compared with the general population.[46] Hypertension is the leading cause of CVD and called "the silent killer" for its harmful effects on vessels, heart and other target organs that progress gradually without any apparent symptoms.[47] Hypertension in RA is multifactorial, involved by chronic inflammation, autoimmunity, and RA-associated lifestyle changes such as limited physical activity and impaired quality of life.[45] Central obesity exacerbated by glucocorticoids in RA has been proved to associate with arterial thickening and stiffening.[48] Moreover, myostatin as a muscle-derived myokine not only leads to muscle atrophy and ectopic fat accumulation, but also plays a role in vascular inflammation, aging, and atherosclerotic damage, which may contribute to hypertension and increased CVD risk.[49] There are numerous evidences in the general population that normal BMI individuals with increased visceral fat mass are insulin-resistant and have increased cardiovascular risks.[50] However, a rare study reported the consequences of abnormal BC in RA patients with normal BMI. Our cross-sectional study showed similar prevalence of hypertension in all RA patients (33.5%) and those with normal BMI (32.2%) compared with previous studies.[43,44] In RA patients with normal BMI, hypertension showed worse functional score, higher rate of overfat, and high risk of 2.5-fold associated with myopenia overlapping overfat. These results indicate that special attention should be paid to hypertension in this subset of RA patients, and the mechanisms underlying myopenia overlapping overfat related CVD mortality need further investigation in RA.

There are several limitations of our study. It was designed as a single-center cross-sectional investigation. However, our study patients showed similar demographic characteristics compared with those in the Chinese Registry of rheumatoid arthritis (CREDIT) from 173 centers in 31 provinces all over China,[19] as we previously reported.[5] The application or not of medications in the previous 6 months instead of detailed doses data was collected in order to avoid recall bias of patients, which limited further analysis of the dose–effect relationship between previous glucocorticoid treatment and myopenia overlapping overfat in normal BMI. In a cross-sectional study, associated factors and outcome measurement in the same timeframe made it scientifically inappropriate to determine the causality between hypertension and myopenia overlapping overfat in normal BMI RA patients. In our study, BC was assessed by BIA method rather than dual X-ray absorptiometry (DXA), which is referred as a gold standard. Since previous data reported comparable accuracy and reliability between BIA and DXA in Western or Asian populations, as well as strengths of BIA including non-radioactive, inexpensive, easy-to-use method, BIA is widely recommended for the clinical setting.[12,51,52] Since the cut-offs of BMI, BF%, and ASMI are defined according to ethnic differences in different populations, a worldwide study would be needed to extend our results. A future large scale multi-community based epidemiological survey on the general population and multicenter prospective studies on RA patients with detailed medications, especially IL-6/JAK-STAT inhibition, and biological elements of muscle and fat metabolism would be needed to investigate the clinical significance and link of the neglected extra-articular manifestation of myopenia overlapping overfat in RA.

In conclusion, myopenia overlapping overfat as an important extra-articular manifestation is common in RA patients even with normal BMI. Those normal BMI RA patients with myopenia overlapping overfat need special attention for their worse disease and associations with glucocorticoid treatment and hypertension. Further prospective studies and researches on treatment of BC improvement and underlying mechanisms are worth exploring in the future.

Acknowledgements

We thank all subjects and medical staff who generously contributed to this study. We thank Yan-Fang Ye from Clinical Research Design Division,

Sun Yat-sen Memorial Hospital, who kindly provided statistical advice for this manuscript.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by National Natural Science Foundation of China (grant no. 81971527 and 81801606), Guangdong Natural Science Foundation (2018A030313541), Guangdong Basic and Applied Basic Research Foundation (grant no. 2019A1515011928), and Science and Technology Program of Guangzhou (grant No. 201904010088).

Author contributions

JZL and CTC 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 DHZ and LD also conceived and participated in its design, advised on the search, read and analyzed documents, and edited the paper. YQM, JDM and QHL participated in clinical assessment and BC measurement of RA patients, and critically revised the manuscript. LFC and ZHY carried out the radiographic assessment and critically revised the manuscript. WMC and XLH participated in BC measurement of control subjects. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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.

Data availability

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

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.

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Supplemental material

Supplemental material for this article is available online.

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