Prevalence and Risk Factors for Bone Loss in Rheumatoid Arthritis Patients from South China: modeled by three methods

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Abstract

Background. To explore the prevalence of bone loss among patients with rheumatoid arthritis and healthy controls and further explored the risk factors for osteopenia and osteoporosis of RA patients.

Methods. A cross-sectional survey was undertaken in four hospitals in different districts in South China. Case records, laboratory tests, and bone mineral density (BMD) results were included. Multivariable logistic regression analysis, least absolute shrinkage, selection operator (LASSO), and random forest (RF) was for exploring the risk factors for osteopenia or osteoporosis in RA patients.

Results. Four hundred five patients with RA and 198 HC were included. RA patients had lower BMD in almost detective sites than healthy controls; the decline of lumbar spine BMD was earlier than HC. RA patients were more likely to comorbid with osteopenia and osteoporosis (*p* for trend <0.001) in the lumbar spine than HC. Higher serum 25-hydroxyvitamin D3 level and using tumor necrosis factor inhibitor in the last year, aging, lower body mass index, and increased serum uric acid were associated with bone loss.

Conclusions. RA patients were more prone and earlier to have bone loss than HC. More attention should be paid to measuring BMD in RA patients aging with lower BMI or hyperuricemia. Besides, serum vitamin D and all three detective sites are recommended to check routinely. TNFi usage in the last year might benefit bone mass.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by persistent synovitis and the progressive destruction of bones and cartilage in multiple joints[1]. Osteoporosis (OP) is a well-known extra-articular complication in patients with RA[2], except for pulmonary involvement, cutaneous manifestations, and cardiovascular disease. The disorder of tumor necrosis factor-α (TNF-α), a key proinflammatory cytokine in RA, can stimulate osteoclastogenesis via receptor activator of nuclear factor kappa B ligand (RANKL) activation. As a result, RA patients with OP increased the risk of osteoporotic fracture (OPF), an outcome that impairs quality of life and leads to mortality[3, 4]. The 1-year cumulative mortality rate due to hip OPF in RA patients was reported to be approximately 20% and significantly higher than that in general population[5]. Accordingly, appropriate management of OP and osteopenia could prevent fragility fracture in patients with RA are crucial to optimize clinical outcome[6].

Studies reported that the frequency of OP in patients with RA is reported from 11% to 38.9 % in the lumbar spine and from 6.3% to 36.2 % in the total hip[3, 4, 7, 8], and the risk of developing into OP in RA patients are nearly twice compared with the general population[3]. Disease-specific risk factors, including glucocorticoids (GCs) treatment, immobilization, and reduced physical activity due to tender joints and muscle weakness, and traditional risk factors, like aging and low body mass index (BMI), were frequently reported[9–12]. TNF inhibitor (TNFi), one of the representative biological disease-modifying anti-rheumatic drugs, has been reported either improvement or stable BMD among TNFi users in several prospective studies[13, 14].

However, insufficient information is available for the frequency of osteopenia and bone mineral density (BMD) distribution in three detective sites in RA patients in China[15–17]. Therefore, we undertook a cross-sectional survey in four hospitals from different South China districts to explore the prevalence of bone loss and investigate BMD's differences among patients with RA and healthy controls (HC). Meanwhile, we further explored the risk factors for osteopenia and OP of RA patients, modeled with conventional logistic regression and another two machine-learning modeling methods to ensure robustness.

Methods

Patients

We included the RA patients in four hospitals from October 2018 to August 2019 in the Third Affiliated Hospital of Sun Yat-sen University, Zhuhai Hospital of Guangdong Chinese Medicine, Ganzhou Municipal Hospital, and Fujian Provincial Hospital; we also contemporarily reviewed randomly-selected healthy-check files from these hospitals. The population of interest was 18 or older and diagnosed with RA (satisfied the 2010 ACR / EULAR classification criteria[18]). For RA patients with more than one admission in the study period, only data from the first admission were analyzed. Exclusion criteria included when participants were unable to answer questions, pregnant, with parathyroid disorders, with a malignant tumor, chronically using medication that could affect bone mineral density like bisphosphonates, vitamin D/calcium supplements, refused to write informed consent or refused to have a dual-energy X-ray absorptiometry (DXA). The principal center was the Third Affiliated Hospital, Sun Yat-sen University. The detailed study flow diagram is shown in Figure 1.

Main outcome variable

BMD, *T*-score, and the *Z*-score of the lumbar spine 2-4, femoral neck, and total hip were collected from DXA reports (Hologic Discovery A densitometer, Badford, MA, USA) after blood samples had been taken. In our study, the diagnosis of BMD is the outcome variable. According to the World Health Organization[19], the definition of the *T*-score and the *Z*-score generates the results of BMD. A *T*-score ≥ -1.0, between -1.0 and -2.5, and ≤ -2.5 represent the expected condition, osteopenia, and osteoporosis, respectively, as a diagnosis standard for men aged and over 50 and postmenopausal women. Meanwhile, the *Z*-score is used for premenopausal women and males aged under 50. A *Z*-score of -2.0 or lower indicates a lower BMD compared to the peers ('score below the expected range for age'). Therefore, either HC or RA patients were divided into two subgroups according to the diagnosing conditions, then stratified these subgroups into five ones by BMD results.

Study factors

Thirty-three independent variables (Table 2) were also collected. Smoking and drinking habits, medical and medication history, and laboratory examinations were taken from each participant's history. Dyslipidemia included hypercholesteremia and hypertriglyceridemia. 'Chronic usage' of non-steroidal anti-

inflammatory drugs (NSAIDs) or GC was defined as consecutively taking these medications at least the last three months. 'Rheumatoid factor positive' was defined when the concentration reached or over 30 IU/ml; anti-cyclic citrullinated peptide antibodies (anti-CCP), antikeratin antibodies (AKA), and anti-RA33 antibodies (RA33) 'positive' was defined when their concentrations were at or over 20 IU/ml. Ethical approval was obtained from the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). The registration no. of ethics approval of the study was [2018]02-283-01. Written informed consent was obtained from all individuals participating in this study.

Sample size

A systematic sampling design was used to select the participants. The sample sizes were estimated by PASS 15 software (https://www.ncss.com), with the statistical power (1-β) set 0.90, type I error (α) set 0.05, and assuming that the prevalence of complicating with OP was 40%[20] among RA patients. The software calculated that a total sample size of at least 312 would suffice. To ensure adequate events of each subgroup, we finally recruited 405 patients with RA and 198 healthy subjects for the present study.

Statistical analysis

Data were manually entered into EpiData (http://www.epidata.dk/) and then imported into Microsoft Office Excel (version 2016). Two physicians rechecked and transferred this data to the R software (version 3.6.1) for analysis. Continuous variables are marked as the mean ± standard error (SD), while discontinuous variables are presented as frequency and percentage. Dependent variables / primary outcomes were the T-score, Z-score, and corresponding diagnoses of BMD of the lumbar spine, femoral neck, and total hip, divided and stratified as mentioned above. A two-tailed t-test was used for comparing normally distributed continuous variables, and the *Kruskal-Wallis H* test was for non-normally distributed ones. *Pearson's* or *Fisher's exact* χ^2-test was performed for categorical variables and the Cochran-Armitage trend test for appropriate ordinal variables. R (version 3.6.1) was used for statistical analyses, and statistical significance was assumed at the $p < 0.05$ level.

Model development

Owing to the inadequate amount of young RA patients, predictive models were only created for RA patients whose BMD was diagnosed with T-score. We took three different approaches of regression model development to ensure the robustness and validity of the regression models: clinical knowledge-driven, conventional logistic regression models (model A), least absolute shrinkage and selection operator (LASSO, model B), and random forest (RF, model C). We separated the data of all subgroups randomly into training sets (70%) and verification sets (30%), with the same positive-event proportion; the training set was for modeling, and the other was for validation, which could be evaluated by C-statistics, calibration slope, and the accuracy.

Model A: We preselected and then entered candidate variables based on existing literature or well-established risk factors into logistic regression models. The final set of variables included only

those with a p-value<0.05 from the regression analysis.

Model B: LASSO is an ideal method to improve multicollinearity[21]. The LASSO procedure underwent 5-fold cross-validation to avoid over-fitting. We entered all 33 candidate variables into the LASSO models.

Model C: Random forest model assembles hundreds of more classification trees with a selection of correlates randomly[22]. We applied all 33 variables into the random forest models. The out-of-bag (OOB) estimates error rates; the Gini index was used to reference the relative permutation importance[23] of the correlates. We selected the important factors by giving the Gini index >5.

Results

Clinical features

Data of 405 patients with RA and 198 HC were included in the first step analysis. Missing data occurred only in part of DXA's detective sites; 12 of 198 healthy subjects (6.1%) included in the first step analysis, and 8 of 405 patients (2.0%) did not have DXA in femoral neck or total hip. The characteristics of the participants are presented in Table 1 and supplementary Figure 1. All our participants were aged at or over 40. The difference in gender composition (p=0.256) and age (60.4±10.4 vs. 59.4±10.3, p=0.275) between HC and patients was not significant. Although the BMI of HC was higher than those with RA (22.8±3.62 vs. 22.1±3.39, p=0.031), the composition of BMI groups[24, 25] showed no significant difference. HC had more postmenopausal women and even those with early menopause than patients with RA (88.4% vs. 70.7%, p <0.001). Serum calcifediol [25(OH)D3] level was lower in patients (65.6±22.1 vs. 76.7±32.9, *p*=0.006); deficiency or more severe status of Vitamin D were also more prevalent in RA patients (64.9% vs. 54.5%, p for trend test =0.046). The median disease duration of RA patients was 5.5[1.5;13.0].

Difference and changing trend of BMD

We divided age into five groups by five years, according to van Staa TP, et al. grouping method[26], for analyzing the difference and changing trend of BMD of each site between HC and RA patients. The detailed analysis showed that except for those were aged 40-45, RA patients in all age groups had lower BMD in lumbar spine 2-4 (supplementary Table 1). BMD of the femoral neck was always lower in patients with RA at all age stages. However, except for patients who were 40-45 and 56-60 years old, BMD of the total hip was significantly lower than HC.

The changing trends of BMD of 3 sites were both fluctuating but overall declining with age (Figure 2a). The most dramatic decline in the BMD of the lumbar spine was found in RA patients aged over 50, and it was 5-year ahead of HC. A similar phenomenon was also found in the BMD of the femoral neck before 50. BMI was positively correlated to BMD in all detective sites for both patients and HC (Figure 2b), especially when BMI≥28 kg/ m2, the BMD of the total hip in RA patients was increased obviously; however, the BMD of the same site in HC dropped

Prevalence of bone loss

Since participants in our study were mid-aged or older, only 93 people were diagnosed with Z-score. We did not find a significant difference between HC and RA patients in any detective site.

In male participants aged at and over 50 and postmenopausal women, we noticed that RA patients were more likely to comorbid with osteopenia (24.1% vs. 32.3%) and OP (48.8% vs. 57.3%, p for trend <0.001) only in the lumbar spine. However, the prevalence of osteopenia and OP in any site, or femoral neck, or total hip showed no difference between cases and controls (Supplementary
Table 2 and Supplementary Figure 2).

Risk factors for bone loss in RA patients

The three modeling approaches for three sites resulted in 18 different sets of variables associated with osteopenia and OP (9 sets of each). Two variables were consistently selected across all models, 'age' and 'BMI' (except 'BMI' in model B of the lumbar spine in osteopenia). Details of models were shown in (Supplementary Table 3). Finally, for osteopenia, model A, Model B, and Model A were the best for the lumbar spine, femoral neck, and total hip, respectively. For OP, model A, model B, and model B were optimal for the lumbar spine, femoral neck, and total hip, respectively. Odd ratios of the selected models were shown in Table 3. Aging was a general risk factor for each site and osteopenia (OR: 1.11~1.17) and osteoporosis (OR: 1.15~1.25). On the contrary, increasing BMI was a common protective factor for BMD (for osteopenia, OR: 0.84-0.88; for OP, OR: 0.62-0.68). Higher serum 25(OH)D3 level was a protective factor for lumbar spine [for osteopenia, OR: 0.99(0.98-1.00); for OP, 0.97(0.96-0.98)] and osteoporosis in femoral neck [OR: 0.98(0.96,0.99)]. Besides, results suggested that using TNFi in the last one year was a protective factor for osteopenia in either the lumbar spine [OR: 0.27 (0.08, 0.84)] or total hip [OR: 0.37 (0.14, 0.93)]. Increased serum uric acid was a risk factor for osteoporosis in total hip [OR: 1.01(1.00, 1.01)].

Discussion

Our study detected that in male participants aged at and over 50 and postmenopausal women, the frequency of osteopenia and osteoporosis in the lumbar spine of in-patients with RA was significantly 1.3-fold and 1.2-fold higher than these in healthy counterparts, respectively. The overall frequency of OP in our study is higher than previous studies, which reported 22.4%-46.8%[27, 28]; osteopenia is in the range of the previous reported 25%~34%[7, 8]. Although the significant prevalence of bone loss was only found in the lumbar spine, it was higher than the previous reported (from 31.5% to 36.2 %)[3, 4].

The age at which BMD of these sites drops sharply arrived earlier in RA patients, especially in the femoral neck. This point is a novel finding of the present study. It suggested that RA patients' turning points to develop into OPF maybe earlier in the femoral neck. However, in China, the femoral neck is not a routine monitoring choice but the lumbar spine. Overall, these findings suggest that the BMD of the femoral neck also needs appropriate and earlier management than the lumbar spine.

Except for well-documented risk factors (increasing age and lower BMI) consistently associated with the risk of osteopenia and osteoporosis among in-patients with RA, TNFi usage in the last one year was found a protective factor for osteopenia in the lumbar spine and total hip. TNF-α, a key proinflammatory cytokine in RA, can stimulate osteoclastogenesis via RANKL activation[29], leading to systemic bone loss. This finding is consistent with most observational studies, which reported either improved or stable BMD among TNFi users[14, 30]. It suggested that using TNFi could not only merely reduce disease activity but also protect BMD.

Sabbagh *et al*.[31] found that the inadequate Vitamin D status has a considerably strong association with disease activity in RA cases, and active RA with anti-CCP positivity was associated with lower BMD[32]. Our finding was similar partially, which indicated the need for proper evaluation of Vitamin D status in these patients to ensure the intake of the recommended amount of Vitamin D, but positive anti-CCP was not associated with bone loss in our study.

Serum uric acid (sUA) was found as a risk factor for reduced BMD in the total hip of RA patients (11.6% patient with hyperuricemia and an sUA mean value of 314.1 ± 103.9 μmol/L, data not shown). Several studies have demonstrated that sUA has bilateral effects on bone health. UA is linked to bone loss in hyperuricemia and gout, especially the increased risk of hip fracture[33, 34]. However, UA is the primary antioxidant in human plasma and accounts for more than 60% of the capacity to scavenge free oxidative radicals[35]; thus, it acts as an antioxidant to prevent bone loss and osteoporosis when in the normal physiologic range[36, 37]. Our finding suggested that in RA patients, proper management of hyperuricemia might benefit their hip bone mineral density, lowering the risk of subsequent osteoporotic fracture, which increases the mortality rate[38] and societal and economic cost[39].

This study has limitations. First, we cannot exclude the possibility of patient selection bias because the three centers participating in this study were tertiary referral centers in South China. Therefore, BMD measurement rates in this study cannot represent the real rate of DXA in our country. Second, clinicians were more prone to advise in-patients with higher disease activity and longer disease duration and healthy subjects with higher well-documented risks to have BMD examinations. Hence, our study revealed a higher prevalence of OP than previously reported. Due to the limitation of sample size and cross-sectional study, a prospective and large-scale follow-up is looked forward to in the future.

In conclusion, RA patients enrolled in the study were more prone and earlier to have bone loss than HC. Our study suggests more attention should be paid to measuring BMD in RA patients aging with lower BMI or hyperuricemia. Besides, serum vitamin D and all three detective sites are recommended to check routinely. TNFi usage in the last year might benefit bone mass.

List Of Abbreviations

RA: rheumatoid arthritis

BMD: Bone mineral density

OP: Osteoporosis

TNF-α: tumor necrosis factor-α

RANKL: receptor activator of nuclear factor kappa B ligand

OPF: osteoporotic fracture

GCs: glucocorticoids

BMI: body mass index

TNFi: TNF inhibitor

HC: healthy controls

ACR: American college of rheumatology

EULAR: European league against rheumatism

DXA: dual-energy X-ray absorptiometry

NSAIDs: non-steroidal anti-inflammatory drugs

anti-CCP: anti-cyclic citrullinated peptide antibodies

AKA: antikeratin antibodies

RA33: anti-RA33 antibodies

SD: standard error

LASSO: least absolute shrinkage and selection operator

RF: random forest

OOB: out-of-bag

25(OH)D3: calcifediol

sCr: serum creatine level

sUA: serum uric acid

Declarations

Ethics approval and consent to participate The study was approved by the ethical approval were obtained from the Ethics Committee of the Third Affiliated Hospital, Sun Yat-sen University. The study was performed following the Declaration of Helsinki principles, and informed consent was obtained from all individual participants included in the study. The ethical registration no. of the study was [2018]02-283-01.

Consent for publication Not applicable.

Availability of data and material Because of the confidentiality of the data used for this study and the strict privacy policy of the Third Affiliated Hospital of Sun Yat-sen University, Zhuhai Hospital of Guangdong Chinese Medicine, Ganzhou Municipal Hospital, and Fujian Provincial Hospital, stating the data be kept among the designated research personnel only. Access to the computer code used in this research is available by request to the corresponding author.

Competing interests The authors declare no conflicts of interest.

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Authors' contributions YLC and WJL contributed to conceiving and design of the study, revised the manuscript. ZRH and LZ contributed equally to draft the manuscript; ZRH was responsible for analyzing the data; ZRH, LZ, ZML was for interpreting the results; ZML, CLZ, HL, SMX, and JJZ contributed to collect data and revise the manuscript. All authors approved the publication.

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Tables

Table 1. Characteristics of the participants

Characteristics	HC, n==198	RA, n=405	*p*
Demographic			
Age, years, mean (SD)	60.4 (10.4)	59.4 (10.3)	0.275
Disease duration, years, median [IQR]	NA	5.5[1.5;13.0]	NA
BMI, Kg/□, mean (SD)	22.8 (3.6)	22.1 (3.4)	0.031
Female, n (%)	146 (73.7)	317 (78.3)	0.256
Menopause status of female, n (%)			<0.001*
Post-menopause, age>45	104 (71.2)	186 (58.7)	
Early menopause, age≤45	25 (17.1)	38 (12.0)	
Lifestyle			
Smoking, ever or current, yes, n (%)	17 (8.6)	36 (8.9)	0.937
Drinking, ever or current, yes, n (%)	18 (9.1)	18 (4.4)	0.035
Medical history			
Diabetes mellitus	35 (17.7)	47 (11.6)	0.055
Hypertension	75 (37.9)	77 (19.0)	<0.001
Coronary heart disease	20 (10.1)	20 (4.9)	0.027
Hyperuricemia	15 (7.6)	43 (10.6)	0.297
Dyslipidemia	58 (29.3)	56 (13.8)	<0.001
Femoral neck necrosis	1 (0.5)	8 (2.0)	0.268
Laboratory			
Serum calcium level, mmol /L, mean (SD)	2.4 (0.2)	2.3 (0.1)	<0.001
Serum phosphate level, mmol /L, mean (SD)	1.9 (8.1)	1.2 (0.4)	0.272
Serum creatinine level, μmol /L, mean (SD)	67.2 (32.9)	62.6 (20.5)	0.086
Serum Uric acid level, μmol /L, mean (SD)	327.9 (101.2)	314.1 (103.9)	0.146
Serum 25(OH)D3 level, nmol /L, mean (SD)	65.6 (22.1)	76.7 (32.9)	0.006
Vitamin D deficiency, yes, n (%)	65 (32.8)	145 (35.8)	0.046*
Hypovitaminosis D, yes, n (%)	43 (21.7)	118 (29.1)	0.046*

*: *p* for trend with Cochran-Armitage test; HC: healthy controls; RA: rheumatoid arthritis; hypovitaminosis D: serum 25(OH)D3 <50 nmol/L; VitD3 deficiency: serum 25(OH)D3 <75nmol/L.

Table 2. Candidate variables

Domains	Variables*
Demographics and lifestyles†	(1) age, (2) BMI, (3) gender, (4) smoker, always or never/seldom, (5) drinking, always or never/seldom
Medical history†	(6) hypertension, (7) diabetes mellitus, (8) coronary heart disease, (9) hyperuricemia, (10) dyslipidemia, (11) femoral neck necrosis
Medication history of RA patients†	(12) chronic NSAIDs usage, (13) chronic GC usage, (14) types of cDMARDs recently taking, (15) TNFi usage in the last one year, (16) disease duration
Laboratory	(17) serum calcium level, (18) serum phosphate level, (19) sCr, (20) sUA, (21) CRP level†, (22) ESR†, (23) rheumatoid factor concentration†, (24) anti-CCP concentration† (25) serum 25(OH)D3 level†, (26) C3 level, (27) C4 level, (28) CH50 level, (29) ANA titer, (30) rheumatoid factor positive, (31) anti-CCP positive, (32) AKA positive, (33) RA33 positive

*All variables were included in statistics-driven (LASSO) and random forest model. Except from variable 1,2,16-29, all variables were categorial or dichotomous.

†Factors selected for the clinical knowledge-preselected model.

BMI: body mass index; NSAIDs: non-steroidal anti-inflammatory drugs; GC: glucocorticoid; cDMARDs: conventional disease-modifying anti-rheumatic drugs; TNFi: tumor necrosis factor-α inhibitor; sCr: serum creatine level; sUA: serum uric acid level; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; anti-CCP: anti-cyclic citrullinated peptide antibodies; AKA: antikeratin antibodies; RA33: anti-RA33 antibodies; C3: complement component 3; C4: complement component 4; CH50: serum total complement activity; ANA: antinuclear antibodies.

Table 3. Odd ratios of variables from selective models of all detective sites

Detective sites	Osteopenia			Osteoporosis		
	Variables	Odd ratios (95%CI)	*p*	Variables	Odd ratios (95%CI)	*P*
Lumber spine	Age	1.15 (1.10, 1.21)	<0.001	Age	1.25 (1.18, 1.33)	<0.001
	BMI	0.88 (0.77, 0.99)	0.038	BMI	0.68 (0.57, 0.79)	<0.001
	Serum 25(OH)D3 level	0.99 (0.98, 1.00)	0.030	Serum 25(OH)D3 level	0.97 (0.96, 0.98)	<0.001
	TNFi usage in the last one year	0.27 (0.08, 0.84)	0.027			
Femoral neck	Age	1.17 (1.12, 1.22)	<0.001	Age	1.26 (1.18, 1.36)	<0.001
	BMI	0.85 (0.77, 0.95)	0.003	BMI	0.62 (0.50, 0.75)	<0.001
	Rheumatoid factor concentration	1.00 (0.99, 1.02)	0.183	Serum 25(OH)D3 level	0.98 (0.96, 0.99)	0.002
				sUA	1.00 (1.00, 1.01)	0.068
				Disease duration	1.00 (0.89, 1.13)	0.967
				Serum phosphate level	1.87 (0.48, 29.95)	0.631
Total hip	Age	1.11 (1.08, 1.15)	<0.001	Age	1.15 (1.10, 1.21	<0.001
	BMI	0.84 (0.77, 0.92)	<0.001	BMI	0.68(0.58,0.78)	<0.001
	TNFi usage in the last	0.37 (0.14,	0.040	sUA	1.01(1.00,	0.001

one year		0.93)	1.01)

BMI: body mass index; 25(OH)D3: calcifediol; TNFi: tumor necrosis factor-α inhibitor; sUA: serum uric acid level

Figures

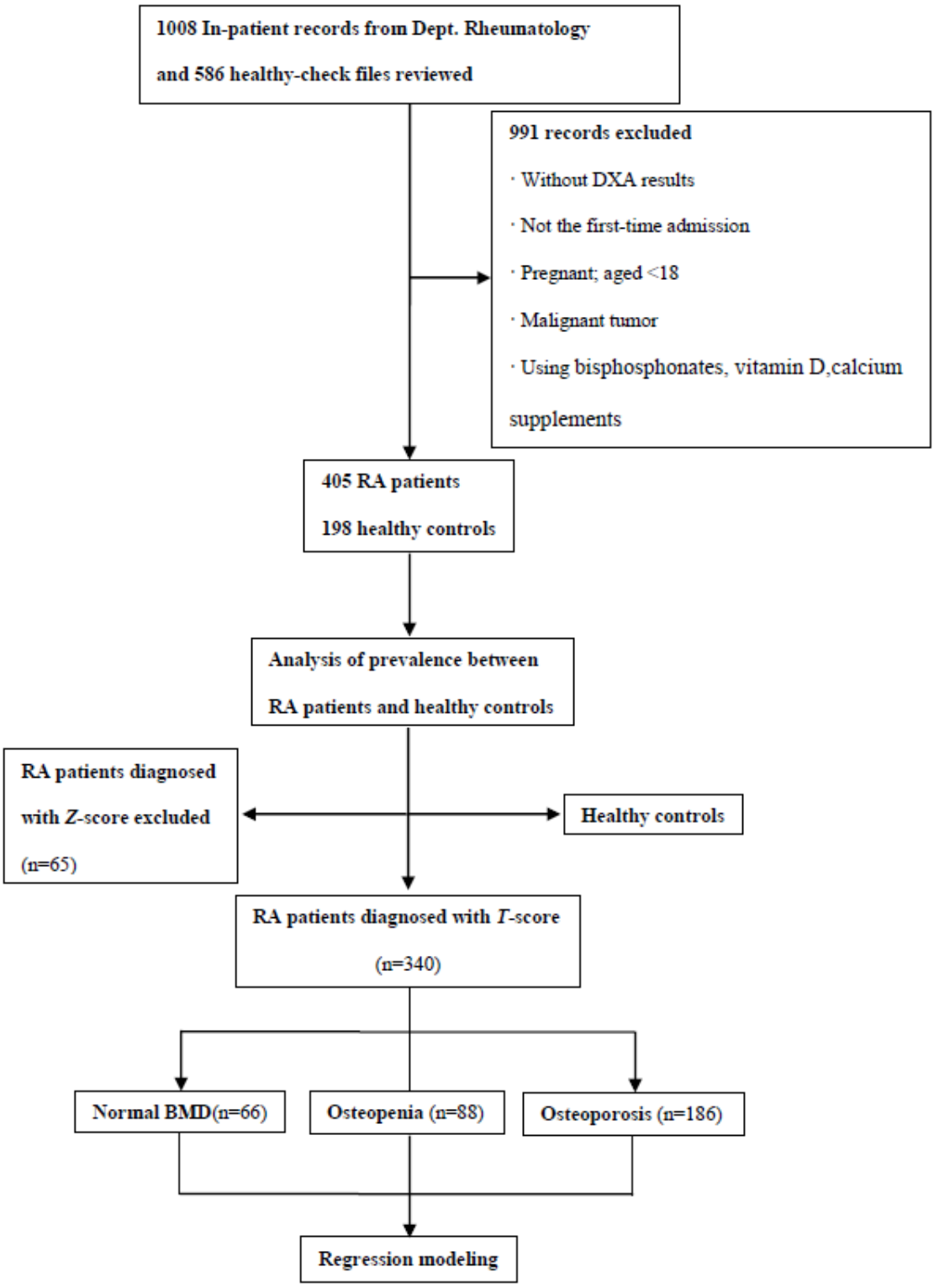

Figure 1

Study flow diagram. Diagnosed with T-score: for those are post-menopausal women and men aged ≥ 50. Diagnosed with Z-score: for those are pre-menopausal women and men aged < 50.

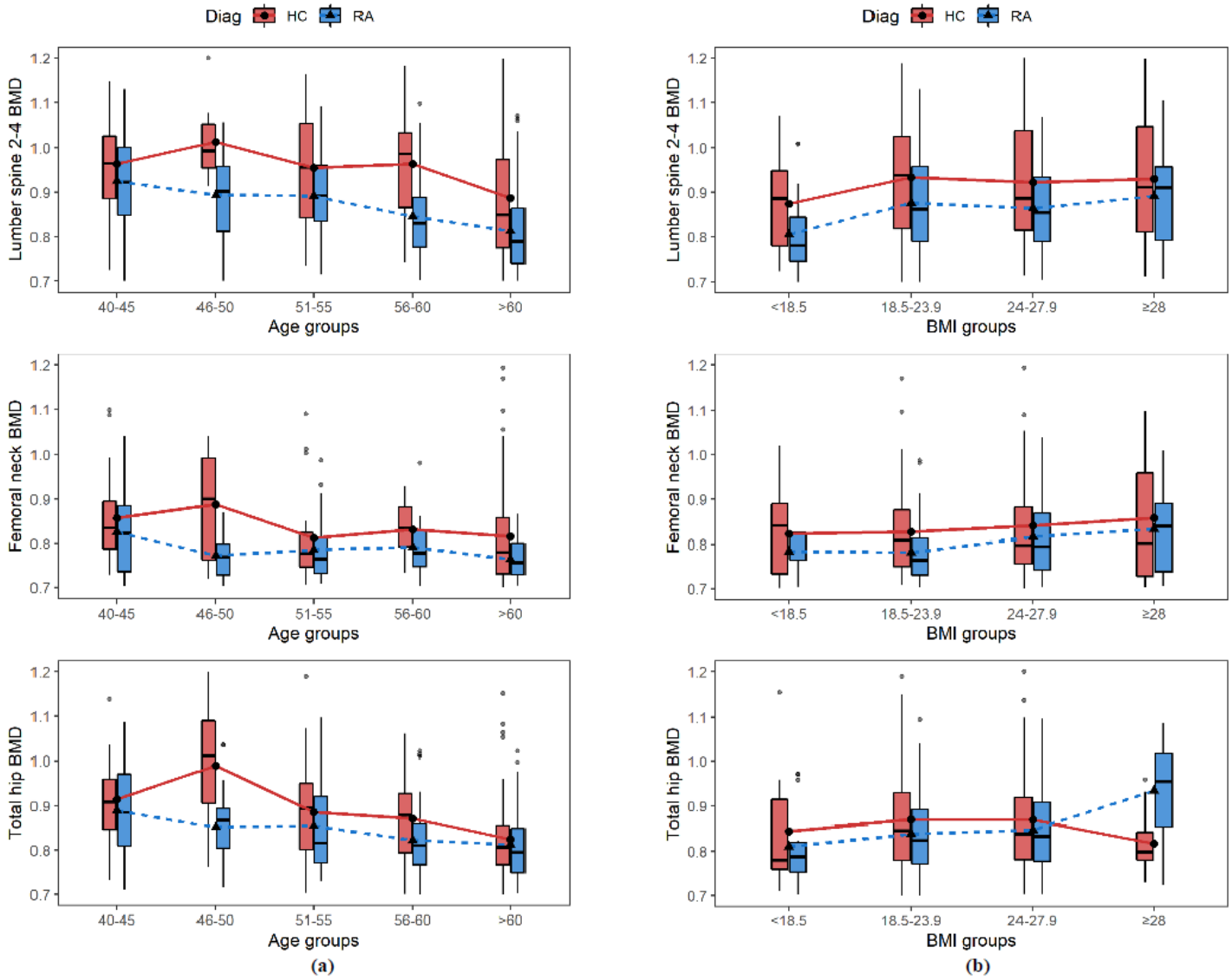

Figure 2

The changing trend of BMD with aging (a) and weight-gaining (b) of patients with RA and HC.

Supplementary Files

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- SupplementaryMaterial.docx