Original Article

Title:

Low serum albumin concentration is associated with increased risk of osteoporosis in postmenopausal patients with rheumatoid arthritis

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Conflict of Interest

KE is affiliated with, and KN supervise the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. KE has received payments for lectures from Amgen, Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Ono, and Pfizer, and received consultant fee from Asahi-Kasei. KE and MH have received research grants from Amgen, Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. YN has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. HT has

received payments for lectures from Asahi-Kasei, Astellas, Chugai, Eisai, Eli Lilly, and Pfizer, and has received a research grant from Chugai. JH have received payments for lectures from Chugai, and research grants from Astellas, Chugai, and Eisai. HY have received research grants from Astellas, Daiichi Sankyo, Eisai, and MSD. KN has received a research grant from Astellas. SO declare that he has no conflicts of interest.

Ethical Statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the institutional ethical review board of our institute (Osaka University; approval No. 18258). The board waived the requirement for patient informed consent by posting the opt-out information in the hospitals' homepage.

Abstract

Background

The risk of osteoporosis in patients with rheumatoid arthritis (RA) is frequently overlooked, and investigating a simple indicator in routine care may be beneficial to motivate osteoporosis examination. The aim of this retrospective, case-controlled study was to identify the correlation between serum albumin concentrations and the prevalence of osteoporosis in postmenopausal patients with RA.

Methods

This study enrolled 197 patients who underwent dual-energy X-ray absorptiometry of lumbar spine (LS) and proximal femur without osteoporosis treatment [mean age, 67.5 years; disease duration, 12.8 years; Disease Activity Score assessing 28 joints with C-reactive protein, 2.0; prednisolone dose, 4.9 mg/day (usage, 42.6 %); and LS T-score, -1.9]. Patients were classified into 2 groups: osteoporosis, defined as ≥ 1 areal bone mineral density T-score ≤ −2.5 or history of fragility fracture of the vertebra or proximal femur (121 patients), and non-osteoporosis (76 patients). Groups were then matched by propensity score using clinical backgrounds affecting bone metabolism.

Results

In non-matched model, serum albumin concentration was significantly associated with osteoporosis-related factors such as aging, inflammation, physical disability, and glucocorticoid dose. Multivariate logistic regression revealed that serum albumin concentration was independently and significantly associated with osteoporosis risk (odds ratio=0.22, 95% confidence interval=0.08, 0.61, p=0.0033). After propensity score matching, 57 patients for each group showed that in addition to the LS and femoral neck T-scores (p<0.001), serum albumin concentrations (p=0.01) remained lower in the

osteoporosis group compared to non-osteoporosis group. Receiver operating characteristic curve analysis in non-matched model revealed that when cut-off value of serum albumin concentration for indicating osteoporosis was set at 4.2 g/dl, the area under the curve was 0.69, sensitivity 0.74, and specificity 0.58.

Conclusions

Low serum albumin concentration was significantly and independently associated with the prevalence of osteoporosis, which may be considered as one of the osteoporosis-related factors in postmenopausal patients with RA.

Introduction

Rheumatoid arthritis (RA) is one of the major causes of secondary osteoporosis [1]. Decreased systemic bone mineral density (BMD) is observed from the early onset [2], and BMD also decreases with disease duration [3]. As a result, RA patients have relatively higher risk of fracture (approximately 1.5- to 2.6-fold higher) than healthy individuals [4]. The importance of a long-term treatment strategy based on early osteoporosis diagnosis has been demonstrated [5, 6], although the risk of osteoporosis in RA is frequently overlooked. Therefore, investigating a simple indicator of osteoporosis in routine care may be beneficial for clinicians to motivate early osteoporosis examination. Many reports have addressed possible factors contributing to progressive bone loss in RA. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-17, cause the expression of receptor activation of nuclear factor κB ligand (RANKL), which leads to osteoclastogenesis and bone loss [7]. Glucocorticoid use leads to decreased BMD [8], and recent reports also demonstrated that high anti-citrullinated peptide antibody (ACPA) titer is associated with higher bone resorption marker concentrations and decreased BMD [9].

In addition, poor nutrition in patients with RA has been correlated with lower BMD [10]. A report in the general population demonstrated that lower serum albumin concentration is associated with the risk of osteoporosis [11]. However, to the best of our knowledge,

no studies have demonstrated the association between serum albumin concentrations and osteoporosis in RA. Our hypothesis of the current study was that low serum albumin concentrations may be independently associated with the risk of osteoporosis, and may be a useful, convenient, surrogate marker to indicate the risk of osteoporosis in RA patients.

Materials and Methods

Study design and participants

This retrospective, case-controlled study was conducted at two centers in Japan: Osaka University Hospital and Nagayama Rheumatology and Orthopaedic Clinic. The diagnosis of RA was based on the 1987 revised American College of Rheumatology (ACR) criteria [12] or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria [13]. The study recruited postmenopausal patients with RA who underwent dual-energy X-ray absorptiometry (DXA) (PRODIGY, GE Healthcare, Madison, WI, USA; Discovery, Hologic, Waltham, MA, USA) for measurement of BMD in the lumber spine (LS) (L1–L4), total hip (TH), and femoral neck (FN), and spinal radiographs to examine vertebral fracture before starting osteoporosis treatment from 2010 to 2017 (Figure 1). Patients were excluded if they had a history of any kinds of osteoporosis treatment (such

as calcium, vitamin D, vitamin K, selective estrogen receptor modulator, bisphosphonates, denosumab, or teriparatide), diseases affecting bone metabolisms such as diabetes, thyroid or parathyroid diseases, hormone replacement therapy, cancer and radiation therapy involving the skeleton, osteomalacia, severe impaired renal function [estimated glomerular filtration rate (eGFR) < 30 (ml/min/1.73 m^2)] or hepatic function (more than double of the standard value of hepatic enzyme), or poor oral ingestion (such as tube feeding). The BMD data were standardized by the correction method proposed by the Japan Osteoporosis Society in reference to the International Society for Clinical Densitometry Guidance [14]. Regions of severe sclerosis, vertebral fracture, and operated sites were excluded from BMD measurements, as previously described [15]. Osteoporosis was diagnosed according to the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011 [16] and the guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research 2004 [17]. Participants were classified into 2 groups: the osteoporosis group, defined as LS, TH, or FN T-scores ≤ -2.5 or a history of previous fragility fracture of vertebra or proximal femur. The others were defined as the non-osteoporosis group. These patient clinical background data were examined: age, duration of RA, body mass index (BMI), Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity

Score in 28 joints with C-reactive protein (DAS28-CRP), and Clinical Disease Activity Index (CDAI), and the use of glucocorticoid (prednisolone equivalent), methotrexate, and biologics. Following laboratory data were also examined: CRP; matrix metalloproteinase-3 (MMP-3); total protein; albumin; total cholesterol; triglycerides; glucose; creatinine; eGFR; creatine kinase; corrected calcium (Ca); 25-hydroxyvitamin D; rheumatoid factor (RF); and ACPA titer and positivity, in addition to N-terminal type I procollagen propeptide (PINP) as a bone formation marker and isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b) as a bone resorption marker [5].

Propensity score matching

To equalize the clinical backgrounds which may affect bone metabolism, we used 1:1 optimal propensity score matching without replacement by age, body mass index, disease duration of RA, DAS28-CRP, glucocorticoid dose, and glucocorticoid usage (which may affect BMD) as previously described [5]. Finally, 57 patients from each group were extracted (Figure 1).

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Comparisons between the

122 osteoporosis and non-osteoporosis groups were performed using the Mann-Whitney U
123 test or chi-squared test. Correlation between the continuous variables were examined by
124 Spearman's rank correlation coefficient. Variables which were previously reported as the
125 risk factors of osteoporosis associated with RA, as well as showing $p<0.1$ between two
126 groups (albumin, age, disease duration, BMI, and MMP-3) were selected as explanatory
127 variables according to the previous report [18]. Then, multivariate logistic regression
128 analysis was performed to identify the factors significantly associated with the risk of
129 osteoporosis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to
130 estimate the relative risk. Receiver operating characteristic (ROC) curves were
131 constructed to determine the best cut-off value of serum albumin concentrations
132 discriminating between the osteoporosis and non-osteoporosis group, and the area under
133 the ROC curve was calculated as a measure of the overall discriminative ability of serum
134 albumin concentrations. The cut-off point was identified as that closest to the (0, 1) point.
135 All tests were performed using the statistics software SPSS (version 22, IBM, Armonk,
136 NY, USA) with $p<0.05$ considered significant.
137
138 *Ethical statement*
139 This study was conducted in accordance with the ethical standards of the Declaration of

Helsinki and approved by the institutional ethical review board of our institute. The board waived the requirement for patient informed consent by posting the opt-out information in the hospitals' homepage.

Results

Patient disposition and characteristics

Among 197 postmenopausal patients with RA who underwent DXA and spinal radiographs without osteoporosis treatment, 121 patients fulfilled the osteoporosis criteria and 76 patients did not (Table 1). Patient characteristics are summarized here: mean age 67.5±10.6 years; RA disease duration 12.8±10.9 years; CRP 0.5±1.2 mg/dL; DAS28-CRP 2.0±1.0; eGFR 72.1±19.6 mL/min/1.73 m^2; RF positivity 60.4%; and ACPA positivity 70.1%; prednisolone dose 4.9 mg/day for 42.6% of participants; methotrexate dose 8.0 mg/day for 62.9%; and biologics for 31.5%. There were significant differences in LS, TH, and FN BMD (g/cm^2 and T-score) (p<0.001), age (p=0.001), duration of RA (p=0.049), body mass index (p=0.009), serum concentration of total protein (p=0.006) and albumin (p<0.001). In addition, there were significant correlations between serum albumin concentration and serum total protein concentration (r=0.24, p=0.001), BMD (g/cm^2) of LS (r=0.21, p=0.0025), TH (r=0.36, p<0.001), and FN (r=0.36, p<0.001), respectively.

158 There were no significant differences in serum concentration of albumin (g/dl; mean ±
159 SD) between non-biologics group (4.0±0.4), tumor necrosis factor inhibitors group
160 (4.2±0.4), tocilizumab group (4.2±0.4), and abatacept group (4.1±0.3) (p=0.15 between
161 groups).
162 Then, multivariate logistic regression analysis revealed that serum albumin concentration
163 was independently and most strongly associated with osteoporosis risk (OR=0.22, 95%
164 CI=0.08, 0.61, p=0.0033], followed by age (OR=1.04, 95% CI=1.01, 1.08, p=0.012) and
165 BMI (OR=0.88, 95% CI=0.80, 0.98, p=0.016) (Table 2).
166 Then, to further clarify these results, 57 participants of each group were extracted by
167 matching clinical backgrounds which may affect bone metabolism using propensity score
168 (Figure 1). Patient characteristics are shown in Table 3 and summarized here: mean age
169 67.0±9.0 years; RA disease duration 12.1±10.4 years; CRP 0.4±0.9 mg/dL; DAS28-CRP
170 2.0±0.9; eGFR 73.2±19.8 mL/min/1.73 m^2; RF positivity 67.5%; and ACPA positivity
171 76.3%; prednisolone dose 4.2 mg/day for 36.0% of participants; methotrexate dose 7.8
172 mg/day for 69.3%; and biologics for 28.1%. Significant differences were noted between
173 the osteoporosis and non-osteoporosis groups in the LS, TH, and FN BMD (g/cm^2 and T-
174 score) (p<0.001). Interestingly, after matching by clinical backgrounds, serum total
175 protein concentrations (7.1 vs. 7.3 g/dL, p=0.04) and albumin concentrations (4.0 vs. 4.2

g/dL, p=0.01) remained significantly lower in the osteoporosis group than in the non-osteoporosis group. Then, multivariate logistic regression analysis revealed that serum albumin concentration was the only factor significantly associated with the risk of osteoporosis (OR=0.24, 95% CI=0.074, 0.77, p=0.017) (Table 4).

In both non-matched and matched model, serum albumin concentrations showed stronger correlation with the prevalence osteoporosis compared to that of total protein. Among the parameters, significant correlations were found between serum albumin concentrations and age (p<0.05), CRP (p<0.001), DAS28-CRP (p<0.001), HAQ-DI (p=0.0015), and prednisolone dose (p=0.018). These results suggest that risk factors of osteoporosis associated with RA such as aging, high disease activity, low physical functional status, and glucocorticoid dose are strongly correlated with serum albumin concentrations, which may comprehensively represent these osteoporosis-related factors.

Cut-off value of serum albumin concentrations for indicating osteoporosis

Figure 2 shows the ROC curve to determine the optimal cut-off value of serum albumin concentrations for indicating osteoporosis. In non-matched model (Figure 2a), the cut-off value was set at 4.2 g/dl, and the area under the curve was 0.69, sensitivity 0.74, and specificity 0.58. In propensity score-matched model (Figure 2b), the cut-off value was set

at 4.2 g/dl, and the area under the curve was 0.62, sensitivity 0.67, and specificity 0.58.

Distribution of serum albumin concentrations and the prevalence of osteoporosis

Figure 3a shows histogram of serum albumin concentrations of non-matched patients. The number of patients with serum albumin concentrations ≤ 4.2 g/dl were 121 and that of > 4.2 g/dl were 76. Figure 3b shows the crude percentage of patients with osteoporosis by categories of serum albumin concentrations in non-matched model. The prevalence of osteoporosis became markedly lower in patients with serum albumin concentrations > 4.2 g/dl compared to that of ≤ 4.2 g/dl.

Discussion

This retrospective, case-controlled study demonstrated the possibility of serum albumin concentration as a simple indicator to motivate further osteoporosis examinations in patients with postmenopausal RA.

Previous reports demonstrated that advanced age, (≥ 60 years), disease duration, disease activity, low body mass index, oral glucocorticoid use, and high modified HAQ as risk factors for osteoporosis in RA patients [1, 19]. Although these studies reported a relationship between osteoporosis and disease activity of RA or medications, serum

albumin concentration was not considered. On the other hand, previous studies have reported the association between hypoalbuminemia and osteoporosis in the general population. Afshinnia et al. demonstrated that odds ratio of osteoporosis in patients with serum albumin of ≤ 3 g/dl was approximately 3.3-fold at the FN (p<0.001) and 2.2-fold at the LS (p<0.001) compared with patients with serum albumin > 4 g/dl after adjustment of clinical backgrounds [11]. Moreover, D'Erasmo et al. reported that low BMD was associated with hypoalbuminemia in patients with disease-related hypoalbuminemia, such as chronic hepatitis or cirrhosis, inflammatory bowel disease, and nephrotic syndrome [20].

The mechanisms of the association between low serum albumin concentration and low BMD is not well understood. One plausible mechanism is that hypoalbuminemia may directly promote osteoclastogenesis and may also inhibit osteogenesis via relationship with nuclear factor-κB [21]. Another proposed mechanism is that albumin has an anabolic effect on bone components via its stimulatory effect on bone calcification and deoxyribonucleic acid contents [22]. In addition, hypoalbuminemia may affect the metabolism of parathyroid hormone and vitamin D binding protein [23], and may also decrease matrix Gla protein resulting in reduced osteoblastic and elevated osteoclast activities [24].

Serum albumin concentrations are affected by disorders such as liver disease, nephrotic syndrome, chronic inflammation, cancer, and malnutrition [25]; in addition, hypoalbuminemia is frequently observed in RA patients. Levick reported that albumin leaks to inflamed joints because of increased vascular–joint albumin permeability, and inflammation is a factor that causes hypoalbuminemia in RA patients [26], and Wilkinson et al. reported hypoalbuminemia was strongly related to disease activity of RA [27]. Concerning inflammation, monocytic products especially interleukin-1 reduced messenger RNA expression and synthesis of albumin in rat hepatocytes [28]. In the present study, there were no significant differences in serum concentration of albumin between non-biologics group and each biologics group, maybe due to well-controlled disease activity on the whole.

On the other hand, glucocorticoid preserved mRNA expression level of albumin in vitro, although didn't show significant effect in the albumin synthesis in vivo [29]. Further investigations may be required to investigate the effects of glucocorticoid on serum albumin concentrations in RA.

Taken together, arthritis may directly induce osteoclastogenesis [30] and inhibit osteogenesis [31] via cytokines such as TNF-α and IL-6, although may also indirectly induce them by hypoalbuminemia. Indeed, serum albumin concentrations significantly

correlated with BMD, which may play a role as a specific surrogate marker of osteoporosis associated with RA. Finally, the ROC curve analysis in both non-matched and propensity score matched model showed that a serum albumin ≤ 4.2 g/dl was the optimal cutoff level for indicating osteoporosis.

This study has several limitations. First, because of the retrospective, observational design, it was difficult to certify whether hypoalbuminemia is a cause or a result of osteoporosis. A large, prospective study is required to confirm these results. Second, as there are many risk factors associated with osteoporosis in RA, serum albumin concentrations should be considered as one of these indicators. Third, this study included patients with relatively long disease duration, well-controlled disease activity, and a low glucocorticoid dose, whose osteoporosis examination or treatment was overlooked by their previous doctors. Therefore, patients with early onset, high disease activity, and a high glucocorticoid dose should be confirmed in another study.

However, a strength of this study is that multivariate logistic analysis and propensity score matching may compensate the variation of confounding factors related to postmenopausal osteoporosis in RA.

Conclusions

Low serum albumin concentration is significantly and independently associated with the prevalence of osteoporosis, and may be considered as one of the osteoporosis-related factors in postmenopausal patients with RA. Patients with low serum albumin concentration, especially values ≤ 4.2 g/dL, may be further examined for osteoporosis at the early stage of consultation.

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Figure legends

Figure 1. Study design and patient flow.

RA = rheumatoid arthritis, DXA = dual-energy X-ray absorptiometry, LS = lumbar spine, TH = total hip, FN = femoral neck, ROC = Receiver operating characteristic, DAS28-CRP = disease activity score assessing 28 joints with CRP.

Figure 2. Receiver operating characteristic (ROC) curve to determine the best cut-off value of serum albumin concentrations (g/dL) to discriminate between the osteoporosis and non-osteoporosis group.

(a) Non-matched model and (b) propensity score-matched model.

AUC = area under the curve.

Figure 3. (a) Histogram of serum albumin concentrations of non-matched patients. (b) Comparison of the crude percentage of patients with osteoporosis by categories of serum albumin concentrations.

Figure 1

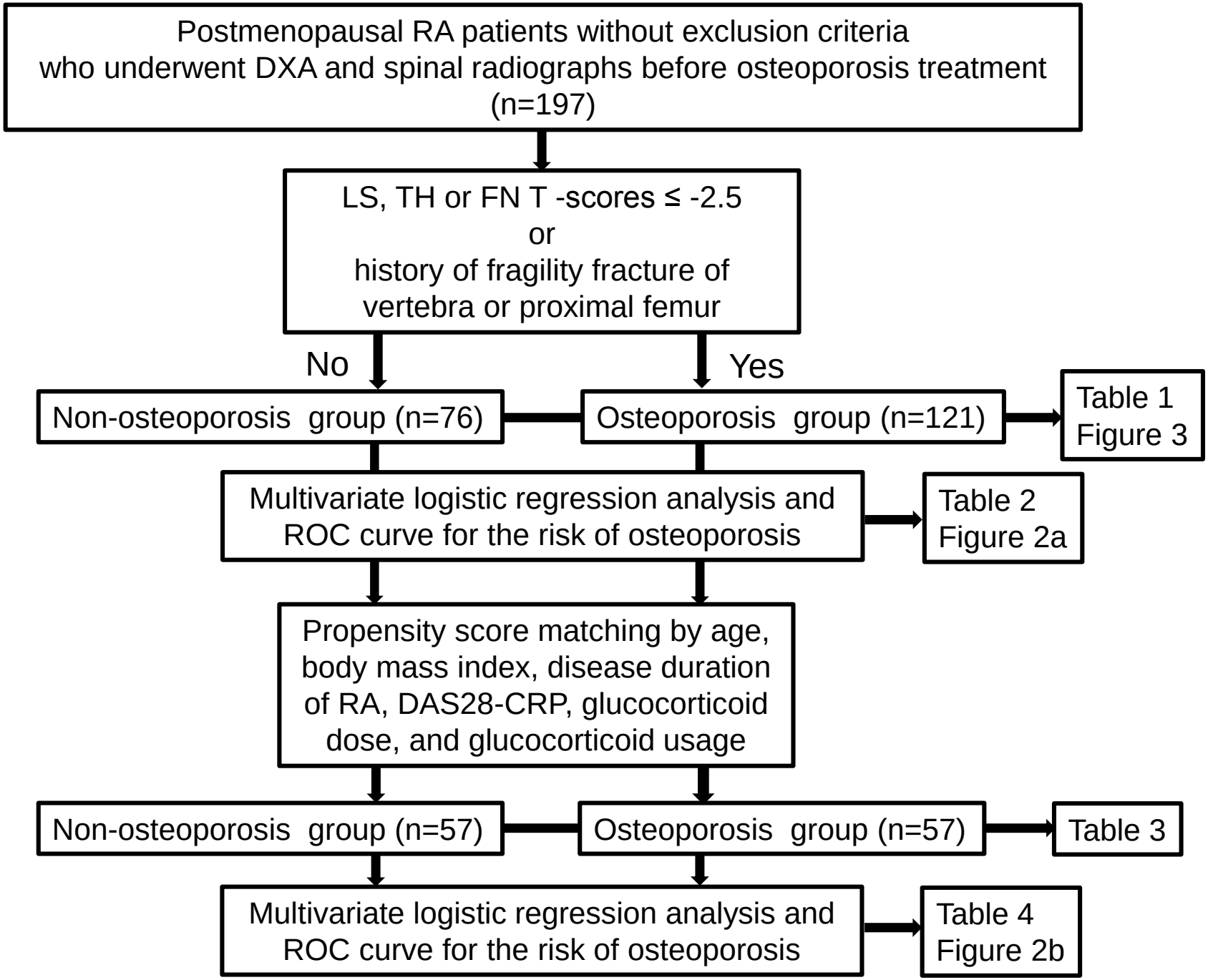
Postmenopausal RA patients without exclusion criteria
who underwent DXA and spinal radiographs before osteoporosis treatment
(n=197)
LS, TH or FN T -scores ≤ -2.5
or
history of fragility fracture of
vertebra or proximal femur
No
Yes
Non-osteoporosis group (n=76)
Osteoporosis group (n=121)
Table 1
Figure 3
Multivariate logistic regression analysis and
ROC curve for the risk of osteoporosis
Table 2
Figure 2a
Propensity score matching by age,
body mass index, disease duration
of RA, DAS28-CRP, glucocorticoid
dose, and glucocorticoid usage
Non-osteoporosis group (n=57)
Osteoporosis group (n=57)
Table 3
Multivariate logistic regression analysis and
ROC curve for the risk of osteoporosis
Table 4
Figure 2b

Figure 2

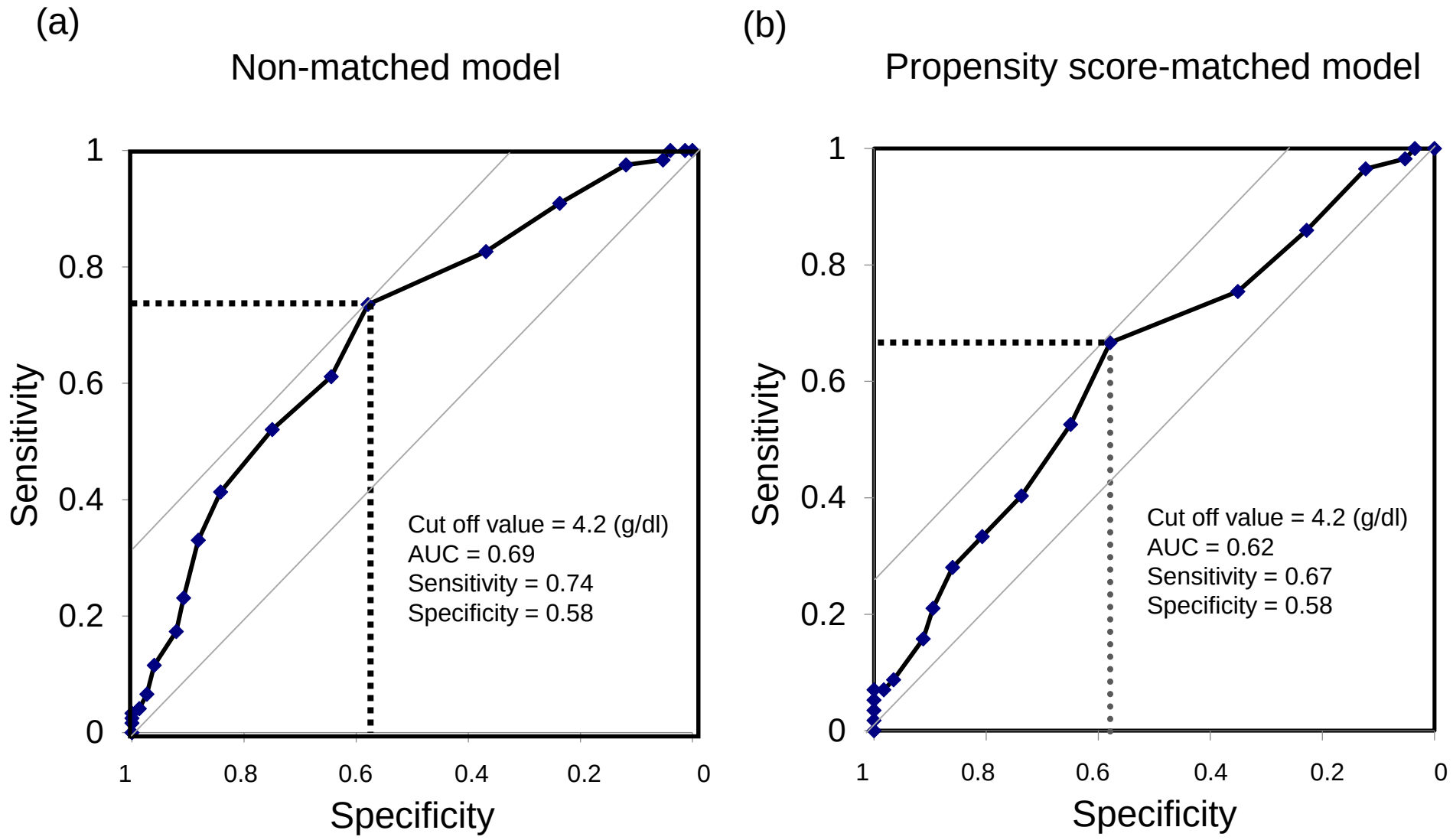
(a)
Non-matched model
Sensitivity
Specificity
1
0.8
0.6
0.4
0.2
0
Cut off value = 4.2 (g/dl)
AUC = 0.69
Sensitivity = 0.74
Specificity = 0.58
(b)
Propensity score-matched model
Sensitivity
Specificity
Cut off value = 4.2 (g/dl)
AUC = 0.62
Sensitivity = 0.67
Specificity = 0.58

Figure 3

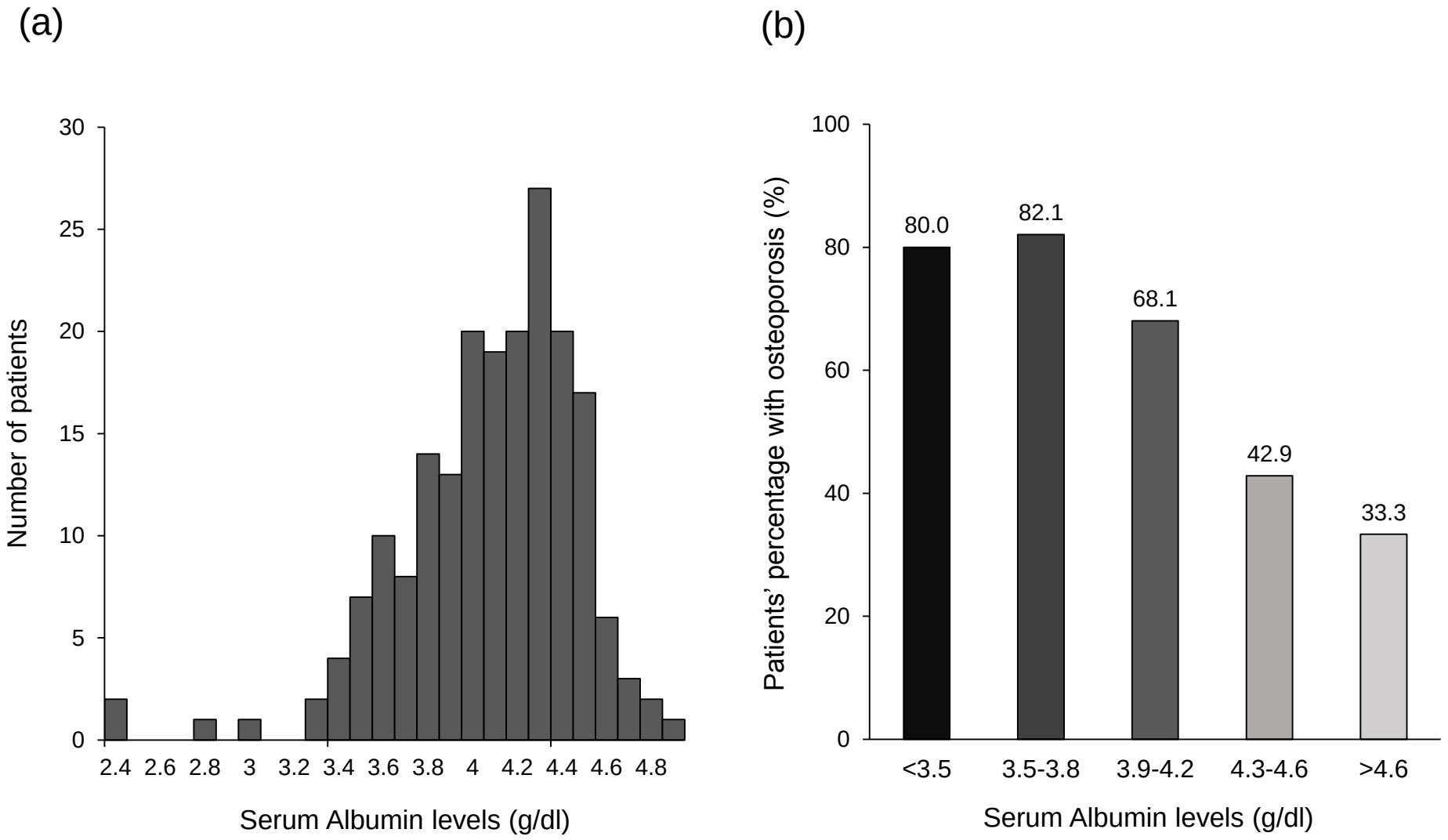
(a)
Number of patients
30
25
20
15
10
5
0
2.4 2.6 2.8 3 3.2 3.4 3.6 3.8 4 4.2 4.4 4.6 4.8
Serum Albumin levels (g/dl)
(b)
Patients' percentage with osteoporosis (%)
100
80
60
40
20
0
80.0
82.1
68.1
42.9
33.3
<3.5
3.5-3.8
3.9-4.2
4.3-4.6
>4.6
Serum Albumin levels (g/dl)

Table 1. Clinical characteristics of the osteoporosis and non-osteoporosis groups in non-matched model

Variable	Osteoporosis group (n=121)	Non-osteoporosis group (n=76)	P value
Age, (mean ± SD years)	69.8±8.9	63.9±12.1	0.001
Duration of RA (years)	14.1±11.3	10.9±10.0	0.049
Body Mass Index (kg/m^2)	21.2±3.2	22.5±3.3	0.009
Lumbar spine BMD (g/cm^2)	0.803±0.147	0.923±0.114	<0.001
Lumbar spine BMD (T-score)	-2.2±1.2	-1.3±0.9	<0.001
Total hip BMD (g/cm^2)	0.634±0.090	0.797±0.084	<0.001
Total hip BMD (T-score)	-2.3±0.8	-1.1±0.7	<0.001
Femoral neck BMD (g/cm^2)	0.555±0.082	0.715±0.080	<0.001
Femoral neck BMD (T-score)	-2.7±0.7	-1.6±0.7	<0.001
Patients with T-score ≤ −2.5, n/N(%)	95/121 (78.5%)	0/76 (0%)	<0.001
Prior vertebral fracture(s), n/N(%)	44/121 (36.4%)	0/76 (0%)	<0.001
Prior proximal femur fracture(s), n/N(%)	9/121 (7.4%)	0/76 (0%)	<0.001
Total protein (g/dl)	7.0±0.5	7.3±0.5	0.006
Albumin (g/dl)	4.0±0.4	4.2±0.3	<0.001
Total cholesterol (mg/dl)	195.8±29.8	206.3±37.0	0.11
Triglyceride (mg/dl)	117.2±77.2	136.4±142.2	0.39
Glucose (mg/dl)	104.4±22.5	102.2±28.3	0.67
Creatinine (mg/dl)	0.66±0.18	0.66±0.17	0.98
eGFR (ml/min/1.73 m^2)	71.6±20.7	72.8±17.8	0.69
Creatine kinase (IU/l)	87.5±82.2	87.9±42.4	0.97
Corrected Ca (mg/dl)	9.2±0.4	9.3±0.4	0.22
PINP (μg/l)	50.8±27.0	44.0±37.6	0.39
TRACP-5b (mU/dl)	401.9±154.5	344.6±162.8	0.20
25-hydroxyvitamin D (ng/mL)	14.0±5.0	14.5±4.5	0.64
CRP (mg/dl)	0.5±1.2	0.4±1.1	0.55
MMP-3 (ng/ml)	127.7±147.1	93.0±119.1	0.10
DAS28-CRP	2.1±0.9	1.9±1.1	0.23
CDAI	5.4±5.0	5.3±8.3	0.99
HAQ-DI	0.90±0.98	0.66±0.67	0.12
RF positivity, n/N (%)	78/121 (64.4%)	41/76 (53.9%)	0.14
RF titer (U/ml)	88.2±223.2	105.6±349.0	0.68
ACPA positivity, n/N (%)	86/121 (71.1%)	52/76 (68.4%)	0.69

ACPA titer (U/ml)	178.1±564.4	123.8±245.1	0.48
Prednisolone dose (mg/day)	5.3±3.0	4.3±2.7	0.15
Prednisolone usage, n/N (%)	54/121 (44.6%)	30/76 (39.5%)	0.48
Methotrexate dose (mg/week)	7.9±2.8	8.2±2.9	0.63
Methotrexate usage, n/N (%)	73/121 (61.3%)	51/76 (67.1%)	0.42
Biologics usage, n/N (%)	38/121 (31.4%)	24/76 (31.6%)	0.98
Biologics (n)	TCZ(11) ABT(7) ETN(9) ADA(3) IFX(3) GLM(4) CZP(1)	TCZ(6) ABT(4) ETN(2) ADA(2) IFX(2) GLM(7) CZP(1)	

Mean ± standard deviation.

n/N (%) = number of patients with measurements / total number of patients (%).

BMD= bone mineral density, eGFR = estimated glomerular filtration rate, Ca = calcium, PINP = Type I collagen N-terminal propeptide, TRAP-5b = Isoform 5b of tartrate-resistant acid phosphatase, CRP = c-reactive protein, MMP-3 = matrix metalloproteinase-3, DAS28-CRP = disease activity score assessing 28 joints with CRP, CDAI= clinical disease activity index, HAQ-DI = health assessment questionnaire disability index, RF = rheumatoid factor, ACPA = Anti-cyclic citrullinated peptide antibody, TCZ = tocilizumab; ABT = abatacept; ETN = etanercept; ADA = adalimumab; IFX = infliximab; GLM = golimumab, CZP = certolizumab pegol.

Differences between the groups were determined by Mann-Whitney U test or chi-square test.

Table 2. Univariate and multivariate logistic regression analysis for the risk factors of osteoporosis in non-matched osteoporosis and non-osteoporosis groups

Variables	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Albumin (g/dl)	0.14 (0.051, 0.36)	<0.001	0.22 (0.08, 0.61)	0.0033
Age (years)	1.06 (1.03, 1.09)	<0.001	1.04 (1.01, 1.08)	0.012
Body Mass Index (kg/m^2)	0.89 (0.81, 0.97)	0.01	0.88 (0.80, 0.98)	0.016
Duration of RA (years)	1.03 (1.00, 1.06)	0.052	1.03 (0.99, 1.06)	0.16
MMP-3 (ng/ml)	1.00 (1.00, 1.01)	0.11	1.00 (1.00, 1.00)	0.64

OR = odds ratio CI = confidence interval.

Table 3. Clinical characteristics of the osteoporosis and non-osteoporosis groups in propensity score-matched model

Variable	Osteoporosis group (n=57)	Non-osteoporosis group (n=57)	P value
Age (years)	66.2±8.0	67.8±9.8	0.35
Duration of rheumatoid arthritis (years)	12.0±9.7	12.2±10.9	0.91
Body Mass Index (kg/m^2)	22.2±3.1	22.1±2.9	0.80
Lumbar spine BMD (g/cm^2)	0.798±0.117	0.908±0.106	<0.001
Lumbar spine BMD (T-score)	−2.3±0.9	−1.5±0.8	<0.001
Total hip BMD (g/cm^2)	0.667±0.076	0.785±0.081	<0.001
Total hip BMD (T-score)	−2.1±0.6	−1.2±0.6	<0.001
Femoral neck BMD (g/cm^2)	0.575±0.074	0.710±0.081	<0.001
Femoral neck BMD (T-score)	−2.6±0.7	−1.7±0.6	<0.001
Patients with T-score ≤ −2.5, n/N(%)	43/57 (75.4%)	0/57 (0.0%)	<0.001
Prior vertebral fracture(s), n/N(%)	23/57 (40.4%)	0/57 (0.0%)	<0.001
Prior proximal femur fracture(s), n/N(%)	5/57 (8.8%)	0/57 (0.0%)	0.02
Total protein (g/dl)	7.1±0.5	7.3±0.5	0.04
Albumin (g/dl)	4.0±0.4	4.2±0.3	0.01
Total cholesterol (mg/dl)	204.2±26.1	203.9±30.6	0.96
Triglyceride (mg/dl)	127.3±90.1	119.7±49.1	0.66
Glucose (mg/dl)	102.0±17.7	101.1±26.3	0.88
Creatinine (mg/dl)	0.64±0.16	0.68±0.19	0.25
eGFR (ml/min/1.73 m^2)	75.5±20.8	71.0±18.3	0.23
Creatine kinase（IU/l)	96.7±93.9	85.2±34.8	0.42

Corrected Ca (mg/dl)	9.3±0.3	9.3±0.4	0.49
PINP (μg/l)	53.2±26.5	43.0±36.2	0.31
TRACP-5b (mU/dl)	392.6±150.3	341.2±161.3	0.33
25-hydroxyvitamin D (ng/mL)	13.7±4.7	14.2±3.8	0.65
CRP (mg/dl)	0.27±0.39	0.47±1.16	0.24
MMP-3 (ng/ml)	92.9±90.2	95.1±130.4	0.92
DAS28-CRP	2.0±0.7	2.0±1.1	0.97
CDAI	5.1±4.7	5.5±8.7	0.81
HAQ-DI	0.70±0.91	0.70±0.68	0.99
RF positivity, n/N (%)	40/57 (70.2%)	37/57 (64.9%)	0.33
RF titer（U/ml)	66.8±136.1	132.4±400.6	0.25
ACPA positivity, n/N (%)	45/57 (78.9%)	42/57 (73.7%)	0.51
ACPA titer（U/ml)	250.8±768.6	143.7±277.3	0.36
Prednisolone dose (mg/day)	4.3±2.3	4.0±2.6	0.69
Prednisolone usage, n/N (%)	22/57 (38.6%)	19/57 (33.3%)	0.56
Methotrexate dose (mg/week)	7.7±2.5	7.9±3.0	0.84
Methotrexate usage, n/N (%)	38/57 (66.7%)	41/57 (71.9%)	0.55
Biologics usage, n/N (%)	15/57 (26.3%)	17/57 (29.8%)	0.68
Biologics (n)	TCZ(3) ABT(2) ETN(4) ADA(3) IFX(1) GLM(1) CZP(1)	TCZ(3) ABT(3) ETN(2) ADA(2) IFX(1) GLM(5) CZP(1)	

Mean ± standard deviation.

n/N (%) = number of patients with measurements / total number of patients (%).

BMD= bone mineral density, eGFR = estimated glomerular filtration rate, Ca = calcium, PINP = Type I collagen N-terminal propeptide, TRAP-5b = Isoform 5b of tartrate-resistant acid phosphatase, CRP =

c-reactive protein, MMP-3 = matrix metalloproteinase-3, DAS28-CRP = disease activity score assessing 28 joints with CRP, CDAI= clinical disease activity index, HAQ-DI = health assessment questionnaire disability index, RF = rheumatoid factor, ACPA = Anti-cyclic citrullinated peptide antibody, TCZ = tocilizumab; ABT = abatacept; ETN = etanercept; ADA = adalimumab; IFX = infliximab; GLM = golimumab, CZP = certolizumab pegol.

Differences between the groups were determined by Mann-Whitney U test or chi-square test.

Table 4. Univariate and multivariate logistic regression analysis for the risk factors of osteoporosis in propensity score-matched model

Variables	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Albumin (g/dl)	0.27 (0.09, 0.79)	0.017	0.24 (0.074, 0.77)	0.017
Age (years)	0.98 (0.94, 1.02)	0.35	0.97 (0.93, 1.02)	0.23
Body Mass Index (kg/m^2)	1.02 (0.90, 1.15)	0.80	1.05 (0.92, 1.20)	0.47
Duration of RA (years)	1.00 (0.96, 1.03)	0.91	0.99 (0.96, 1.03)	0.68
MMP-3 (ng/ml)	1.00 (1.00-1.00)	0.92	1.00 (1.00, 1.00)	0.41

OR = odds ratio CI = confidence interval.