EXTENDED REPORT

Clinical decision rules in rheumatoid arthritis: do they identify patients at high risk for osteoporosis? Testing clinical criteria in a population based cohort of patients with rheumatoid arthritis recruited from the Oslo Rheumatoid Arthritis Register

G Haugeberg, R E Ørstavik, T Uhlig, J A Falch, J I Halse, T K Kvien

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See end of article for authors' affiliations

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Correspondence to:
Dr G Haugeberg, Rheumatology Department, Leeds University, Old Nurses Home, Leeds General Infirmary, Great George Street, Leeds LSI 3EX, UK; glennhaugeberg@operamail.com

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Background: Preliminary clinical criteria based on age, inflammation, and immobility have been proposed to identify which patients with rheumatoid arthritis (RA) should be examined by dual energy *x* ray absorptiometry (DXA) to diagnose osteoporosis. The three item criteria have not been evaluated in male patients with RA or in the entire female RA population.

Objectives: (1) To test the proposed criteria in a cohort of men and women thought to be representative of the entire underlying RA population. (2) To develop clinical decision rules, which could be applied to all patients with RA irrespective of corticosteroid use.

Methods: Clinical and demographic data were collected from a total of 287 representative patients with RA (235 (82%) women, 52 (18%) men, age range 25.3–73.1 years) from the Oslo RA register (completeness 85%). Bone mineral density (BMD) was measured in spine L2–4 (anterior-posterior view) and femoral neck by DXA. The criteria were applied and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results: Mean age (SD) for the women and men with RA was 56.8 (11.0) years and 61.5 (10.2) years; disease duration was 15.5 (9.5) years and 14.7 (8.6) years. Of the women 163 (69%) were postmenopausal. One hundred and seventeen (50%) women and 28 (54%) men fulfilled the three item criteria. For the diagnosis of osteoporosis (T score ⩽−2.5) using the original three item criteria sensitivity in women and men was 74% and 67%, specificity 57% and 50%, PPV 32% and 29% and NPV 89% and 83%, and including weight and ever use of corticosteroids in a five item criteria sensitivity increased to 82% and 83%, specificity decreased to 45% and 45%, PPV was 29% and 31%, and NPV was 90% and 90% respectively.

Conclusion: The novel five item criteria (age, weight, inflammation, immobility, and ever use of corticosteroids) are a more accurate tool to identify patients with RA and osteoporosis than the original three item criteria (age, inflammation, and immobility). The clinical decision rules have an acceptable sensitivity and provide a practical tool for the doctor to identify patients with RA who should have a DXA measurement performed.

I n the rheumatoid arthritis (RA) population osteoporosis is more often found than in the normal population,[1 2] and both inflammation, decreased functional capacity,[3 4] and corticosteroids[5] have been identified as independent risk factors for osteoporosis.

Dual energy *x* ray absorptiometry (DXA) is the gold standard for assessing bone density, and the World health Organisation (WHO) definition of osteoporosis is based on this.[6] In clinical practice, patients with RA with reduced bone density or osteoporosis could be identified either by a screening method or by a case identifying strategy measuring only patients at increased risk for osteoporosis. Although bone densitometry is the method of choice for detecting low bone density, its use may be limited by the availability of equipment, cost, and reimbursement issues. Valid decision rules to identify patients with RA at high risk for osteoporosis based on demographic and clinical risk factors could therefore be of clinical importance by targeting the use of DXA to patients with a high probability of having osteoporosis. For osteoporosis induced by corticosteroids separate guidelines have been published.[7]

Preliminary criteria to identify patients at increased risk of having osteoporosis based on age (women >50 years and men >60 years), disease activity (persistently increased C reactive protein (CRP) ⩾20 mg/l, or erythrocyte sedimentation rate (ESR) ⩾20 mm/1st h), or both and functional status (Steinbrocker score ⩾3 or Health Assessment Questionnaire (HAQ) score ⩾1.25) have been proposed by Lems and Dijkmans.[8] Patients who fulfilled two out of three of the above criteria were considered to require a DXA bone density measurement at hip and spine to diagnose osteoporosis. The criteria have recently been tested by Nolla *et al*[9] in a series of consecutive postmenopausal patients with RA attending an outpatient clinic. The proposed criteria have so far not been tested in patients with RA thought to be representative of the

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Table 1 Clinical data in patients with RA suggested to be representative for the entire RA population

	All (n=287)	Women (n=235)	Men (n=52)
Demographic variables:			
Age (years)	57.6 (11.0)	56.8 (11.0)	61.5 (10.2)
Body weight (kg)	68.4 (12.9)	65.8 (11.5)	80.2 (12.4)
Body height (cm)	167.8 (7.8)	165.5 (5.9)	178.2 (6.8)
BMI (kg/m²)	24.2 (4.1)	24.0 (4.2)	25.2 (3.2)
Menopause	–	163 (69.4%)	–
Menopause age (years)	–	48.7 (4.8)	–
Current smoker (n=282)*	100 (35.5%)	80 (34.6%)	20 (39.2%)
Disease variables:			
Disease duration (years)	15.4 (9.4)	15.5 (9.5)	14.7 (8.6)
RF positive (n=269)*	134 (49.8%)	109 (50.0%)	25 (49.0%)
Global assessment score (VAS 0–100 mm) (n=259)*	23.7 (18.7)	23.7 (18.4)	23.7 (20.0)
HAQ (range 0–3)	0.99 (0.67)	1.01 (0.66)	0.91 (0.70)
mHAQ score (range 1–4)	1.60 (0.51)	1.61 (0.52)	1.55 (0.48)
Mean ESR† (n=285)*	20.8 (15.9)	20.7 (15.5)	21.4 (17.7)
Mean CRP† (n=238)* (mg/l)	15.8 (13.0)	15.3 (12.0)	18.0 (16.3)
Treatment variables:			
Current prednisolone use (n=287)	125 (44%)	102 (44%)	23 (44%)
Ever prednisolone use (n=287)	189 (66%)	157 (667)	32 (62%)
Duration of prednisolone use among current users (months) (n=122)	Median 78 (range 1–500)	Median 84 (range 1–480)	Median 60 (range 18–500)
Cumulative prednisolone dose in past 12 months (g) (n=129)	2.1 (1.4)	2.1 (1.4)	2.1 (1.5)
Current use of oestradiol (n=230)*	–	88 (38%)	–
Current use of any antiresorptive osteoporosis treatment‡ (n=283)*	107 (38%)	104 (45%)	3 (6%)

Except where otherwise indicated, values are mean (SD).
*The number varies from 287 in all patients or from 235 in women patients owing to missing values; †the mean ESR and CRP values are based on two measurements performed two years apart; ‡oestradiol, bisphosphonates or calcitonin; BMI=body mass index; RF=rheumatoid factor positive; VAS=visual analogue scale; HAQ=Health Assessment Questionnaire, mHAQ=modified Health Assessment Questionnaire; ESR=erythrocyte sedimentation rate; CRP=C reactive protein.

entire RA population. In male patients with RA the criteria have not been tested at all.

The first aim of this study was to evaluate the proposed three item criteria in a cohort of men and women with RA suggested to be representative of the entire RA population. The second aim was to examine modified versions of the proposed criteria including weight[1 2] and the use of corticosteroids,[10 11] both well known risk factors for osteoporosis in patients with RA, in an attempt to develop decision rules which could be applied to all patients with RA irrespective of corticosteroid use.

METHODS
Study population
We have previously published cross sectional data on bone mineral density (BMD) and risk factors for osteoporosis in 394 women[1] and 94 men[2] with RA, age 20–70 years, recruited from the Oslo RA register, validated to be complete at the 85% level.[12] As previously described, the examined women were representative[1] and the men[2] fairly representative compared with the register population. At that time neither the HAQ nor the Steinbrocker score was used, which made it impossible to precisely test the proposed criteria by Lems and Dijkmans.[8] However, based on our cross sectional data a clinical algorithm was developed to identify female patients with RA at high risk of osteoporosis.[13] At a two year follow up of the original cross sectional study populations the HAQ was also included as a measurement of disability, making it possible to test the proposed criteria of Lems and Dijkmans.[8] The follow up examination had an attendance rate of 75% (298 women, 68 men). No statistically significant difference was found between baseline and follow up values for attendants and non-attendants for demographic variables and common measures of disease activity and severity, except for age and disease duration due to the two years of follow up. From this follow up cohort of 366 patients a total of 287 (78%) patients (235 women, 52 men) had a complete data set of BMD measurements performed at both hip and spine, HAQ at follow up, and ESR or CRP (measured at both baseline and at two year follow up). This

cohort was found to be representative of the RA register population for demographic (age, disease duration), common measures for disease activity (for example, disease activity score (DAS), ESR, CRP, 28 tender and swollen joint count), and disease severity (modified HAQ, Larsen score of the hands) variables and the use of prednisolone and disease modifying antirheumatic drugs (DMARDs). The only significant difference between our study and non-study patients was found for age (57.6 v 52.3 years, p=0.001) in men and ESR (15.4 v 19.6 mm/1st h, p=0.027) in women. The RA cohort in the present study was therefore considered to be fairly representative of the entire underlying RA population.

The collection of data has previously been extensively described.[1 2 13] The HAQ (eight items, score range 0–3, with higher scores indicating worse disability)[14] was used. The CRP and ESR values, calculated as the mean from the baseline and the two year follow up values, were used as inflammatory indices in the proposed criteria.

For each patient we evaluated the criteria below. To fulfil the criteria proposed by Lems and Dijkmans[8] two out of the three items had to be present: (a) high disease activity, defined as mean CRP above 20 mg/l, or mean ESR above 20 mm/1st h, or both; (b) high age, defined for women as >50 years and for men as > 60 years; and (c) immobility, defined as HAQ ≥1.25.

We also tested a modified version of the proposed criteria by including weight[1 2] and the use of corticosteroids (current and ever use of corticosteroids tested separately),[1 10 11 15] both well known risk factors for osteoporosis in patients with RA. A cut off of 60 kg for the weight criteria was arbitrarily chosen based on validated clinical decision rules for BMD tested in postmenopausal women.[16 17] Owing to lack of decision rules for men we applied the same weight cut off limit as was used in decision rules for postmenopausal osteoporosis.

Bone measurements
Standardised BMD measurements at the left femoral neck and the lumbar spine L2–4 (anterior-posterior view) were performed using DXA (Lunar Expert, Madison, WI, USA). The right hip was measured in six patients.

Table 2 Mean (95% CI) bone mineral density (BMD), T score and Z score in patients with RA suggested to be representative for the entire RA population

	All (n=287)	Women (n=235)	Men (n=52)
BMD (g/cm²):			
Femoral neck	0.851 (0.834 to 0.868)	0.848 (0.828 to 0.867)	0.868 (0.833 to 0.904)
Spine L2–4	1.120 (1.097 to 1.143)	1.108 (1.083 to 1.134)	1.171 (1.116 to 1.227)
Z score (SD):			
Femoral neck	−0.25 (−0.37 to −0.13)	−0.17 (−0.30 to −0.03)	−0.63 (−0.88 to −0.39)
Spine L2–4	0.20 (0.02 to 0.39)	0.31 (0.11 to 0.50)	−0.26 (−0.71 to 0.18)
T score (SD):			
Femoral neck	−1.18 (−1.33 to −1.04)	−1.10 (−1.27 to −0.94)	−1.55 (−1.83 to −1.28)
Spine L2–4	−0.73 (−0.92 to −0.54)	−0.76 (−0.98 to −0.55)	−0.57 (−1.03 to −0.11)

The long time spine phantom precision for the DXA machine calculated as the coefficient of variation (CV%) was 0.8%. The in vivo precision of BMD assessed by duplicate measurements in 42 healthy hospital workers performed by four technicians was 1.7% for the femoral neck, and 2.4% at the lumbar spine L2–4. The within observer variation for our technicians analysing the same scan varied from 0.5% to 1.6% at the femoral neck, and from 0.9% to 1.8% for spine L2–4.

Data analyses, definitions, and statistics

The DXA measurements were expressed as BMD (g/cm²), T score, and Z score. The T score (comparison with normal subjects of the same sex with peak bone mass) and the Z score (comparison with age and sex matched normal controls) were based on a large European and United States reference database for BMD, extensively described in previous studies.[1][2]

Group comparisons were performed with a two tailed unpaired Student's *t* test or Pearson's χ^2 test. A 2×2 table was used to evaluate the sensitivity, the specificity, and the positive (PPV) and negative predictive values (NPV) of the proposed criteria for T score ≤ −1.0, T score ≤ −2.5 (WHO definition for osteoporosis in women[6] here also applied to men), and Z score ≤−1.0. A patient was designated to the BMD reduction category if the BMD loss criterion was reached at either femoral neck or spine L2–4.

All analyses were performed with the SPSS (Statistical Package for Social Sciences) program, version 9.0 (SPSS, Chicago, IL, USA).

p Values≤0.05 were considered significant.

Ethics and legal aspects

The local ethics committee approved the study. The Data Inspectorate had approved the register of patients with RA in Oslo.

RESULTS

Patient and BMD characteristics

Table 1 shows the patient characteristics for various demographic, disease related and treatment variables for the study RA population. Table 2 shows the BMD, T score, and Z score results for the different measurement sites.

A total of 15% of the patients (35 (15%) women and nine (17%) men) had osteoporosis (T score ≤−2.5) at femoral neck, 14% (34 (15%) women and seven (13%) men) at spine L2–4 and at the femoral neck and/or spine 22% (50 (21%) women and 12 (23%) men). The corresponding results for T score ≤−1.0 were 61% (135 (57%) women and 39 (75%) men), 43% (104 (44%) women and 20 (38%) men), 67% (151 (64%) women and 42 (81%) men), and for z score ≤−1.0 26% (58 (25%) women and 16 (31%) men), 22% (47 (20%) women and 17 (33%) men) and 35% (79 (34%) women and 22 (42%) men). In our study population a total of 33% of the patients (84 (36%) women and 10 (19%) men) had a normal BMD

applying the WHO criteria (T score >−1.0) at both the lumbar spine and femoral neck.[6]

Three item criteria by Lems and Dijkmans[8]

A total of 51% of the patients (117 (50%) women and 28 (54%) men) fulfilled two out of the three proposed criteria from Lems and Dijkmans,[8] whereas 19% (46 (20%) women and seven (14%) men) fulfilled all three criteria. In 73% of the patients (173 (74%) women and 35 (67%) men) the age criterion was fulfilled, in 44% (104 (44%) women and 22 (42%) men) the disease activity criteria, in 35% (82 (35%) women and 18 (35%) men) the immobility criteria and in 18% of the patients (39 (17%) women and 12 (23%) men) none of the criteria were fulfilled.

Table 3 shows the sensitivity, specificity, PPV, and NPV of the proposed criteria to identify patients with a T score ≤−1.0, osteoporosis (T score ≤−2.5), and Z score ≤−1.0 for the whole study population and for subgroups of patients according to

Table 3 Sensitivity, specificity, and predictive values of the proposed criteria by Lems and Dijkmans[8] for the bone density cut off categories T score ≤−1.0, T score ≤−2.5 (World Health Organisation osteoporosis definition[6]), and Z score ≤−1.0 tested on all 287 patients with RA and on subgroups of patients according to sex (235 women and 52 men) and menopausal status (72 premenopausal and 163 postmenopausal)

	T score ≤−1	T score ≤−2.5	Z score ≤−1
Sensitivity (%):			
All	59	73	58
Women	59	74	61
Premenopausal	26	75	35
Postmenopausal	68	74	71
Men	57	67	50
Specificity (%):			
All	66	56	54
Women	67	57	56
Premenopausal	83	82	86
Postmenopausal	51	42	42
Men	60	50	43
PPV (%):			
All	78	31	41
Women	76	32	41
Premenopausal	53	20	53
Postmenopausal	79	33	39
Men	86	29	39
NPV (%):			
All	44	88	70
Women	47	89	74
Premenopausal	60	98	74
Postmenopausal	36	80	74
Men	25	83	54

PPV=Positive predictive value; NPV=negative predictive value.

Table 4 Sensitivity, specificity, and predictive values of a modified five item criteria including age, weight, disease activity, immobility, and ever use of corticosteriods for the bone density cut off categories T score ≤−1 SD, T score ≤−2.5 SD (World Health Organisation osteoporosis definition[6]), and Z score ≤−1 SD tested on all 287 patients with RA (n=287), and on subgroups of patients according to sex (235 women and 52 men) and menopausal status (72 premenopausal and 163 postmenopausal)

	T score ≤−1 SD	T score ≤−2.5 SD	Z score ≤−1 SD
Sensitivity (%):			
All	70	82	70
Women	70	82	72
Premenopausal	42	100	52
Postmenopausal	77	80	80
Men	67	83	64
Specificity (%):			
All	56	45	45
Women	56	45	46
Premenopausal	78	74	80
Postmenopausal	35	29	30
Men	60	45	40
PPV (%):			
All	76	29	41
Women	74	29	40
Premenopausal	59	18	55
Postmenopausal	77	31	38
Men	88	31	44
NPV (%):			
All	47	90	73
Women	51	90	76
Premenopausal	64	100	78
Postmenopausal	35	79	74
Men	30	90	60

PPV=Positive predictive value; NPV=negative predictive value.

sex and menopausal status. In patients who had never used corticosteroids, sensitivity was lower and specificity higher than for the whole group, irrespective of sex. For a T score ≤−1.0 sensitivity was 34% (women 38% and men 20%) and specificity 83% (women 86% and men 71%), for a T score ≤−2.5 42% (women 40% and men 50%) and 77% (women 76% and men 80%) and for a Z score ≤−1.0 32% (women 37% and men 17%) and 77% (women 77% and men 73%), respectively (data not shown).

Modified criteria of Lems and Dijkmans[8]
In modified versions of the proposed criteria we included weight and use of corticosteroids (current use and ever use tested separately in the model). In the modified five item criteria including weight and current use of corticosteroids (three out of five items to be fulfilled) an improvement was achieved for sensitivity (women 76% and men 83%) with a somewhat decreased specificity (women 54% and men 50%) for identifying patients with osteoporosis, compared with the proposed three item criteria. By replacing current use with ever use of corticosteroids in the model the sensitivity further increased to 82% and specificity decreased to 45% (table 4).

In a four item criteria assessment, with only weight and not use of corticosteroids in the model (two out of four items to be fulfilled) sensitivity was as high as 85% (women 82% and men 100%), but specificity as low as 32% (women 32% and men 30%).

DISCUSSION
In the present population based study we found a lower sensitivity (74%) and a higher specificity (57%) than Nolla *et al* did in their study evaluating the proposed clinical criteria by Lems and Dijkmans[8] to identify women with RA and

osteoporosis (T score ≤−2.5).[9] In their study, examining post-menopausal patients with RA attending an outpatient clinic, the sensitivity was 86% and specificity 43%. For reduced bone mass, defined as a T score ≤−1 and Z score ≤−1, the differences between the Spanish study[9] and ours were in the same range. Patients in the Spanish study[9] were older, had a more severe disease reflected by measures of disease activity (ESR and CRP) and physical disability (HAQ), compared with the patients in the present study, which most likely explains the differences seen in sensitivity and specificity between the two studies.

When applying the decision criteria by Lems and Dijkmans,[8] about every fourth (13/50)woman in Oslo with RA and osteoporosis at either the femoral neck or lumbar spine would be missed. For specificity, 80 (43%) out of a total of 185 patients without osteoporosis would have been identified as candidates for BMD measurements.

Also, for the first time men with RA were evaluated by the proposed criteria.[8] In men with RA both sensitivity (67%) and specificity (50%) tended to be lower than for women(74% and 57%, table 3). However, the precision of these estimates for the male patients was more uncertain due only to the smaller number included. In our cohort of patients the T score and Z score were lower in men than in women with RA. This is probably due to the higher use of antiresorptive treatment (for example, oestradiol and bisphosphonates) among the women. In a recent two year follow up study of patients with RA recruited from the same Oslo RA register BMD loss at the spine and hip was most pronounced in men who were less aggressively treated with antiresorptive drugs.[18]

The proposed criteria by Lems and Dijkmans[8] is an attempt to identify those patients with RA at high risk for osteoporosis who in a case finding strategy should be selected for DXA bone measurement to diagnose reduced bone density or osteoporosis as defined in the WHO criteria.[6] The three criteria—age, inflammation, and immobility—cover major aspects thought to be involved in the pathogenesis of osteoporosis in RA.[1 3 4] Both numbers of chosen criteria (three items), the criteria thought to cover inflammation (ESR or CRP) and immobility (HAQ or Steinbrocker score), and cut off values for these variables were arbitrarily chosen.[8] However, age,[1 2] inflammation measured by ESR or CRP,[3 4] and HAQ[1 3 4] have all been identified as independent factors associated with reduced bone density or osteoporosis in RA. Measurement of ESR and CRP (measurement of disease activity) and the HAQ (measurement of immobility) may not be the best markers to reflect inflammation and immobility as risk factors for osteoporosis in patients with RA. For example, hand and feet *x* ray Larsen damage scores, suggested to be a marker of cumulative disease activity in cross sectional studies, have been reported to be more strongly associated with osteoporosis than both CRP and ESR.[19 20] The inflammation criterion by Lems and Dijkmans is defined as a persistently increased ESR (≥20 mm/1st h) or CRP (≥20 mg/l).[8] In our study the inflammation criteria were based on the mean value of two measurements taken two years apart. This might have biased our results. However, the mean values obtained at baseline and follow up did not differ substantially either for ESR (20.4 *v* 21.3 mm/1st h) or CRP (15.9 *v* 15.8 mg/l). Interestingly, Wolfe and Pincus recently found that the level of inflammation measured by ESR remained stable over the long term course of RA.[21]

The alternative to a case finding strategy to diagnose patients with osteoporosis according to the WHO criteria[6] using DXA is to screen all patients. This strategy is not recommended in primary osteoporosis.[22] Different simple decision rules, based solely on patient derived data, have been constructed to identify postmenopausal women with low BMD recommended to have a DXA measurement performed.[16 17] The SCORE (simple calculated osteoporosis risk estimation) is a scoring tool based on six questions (age, weight, race, fracture history, RA history, and oestrogen use)[16]

and the ORAI (osteoporosis risk assessment instrument), a simple algorithm, is only based on age, weight, and current oestrogen use.[17] These clinical instruments (sensitivity about 95%) identify the vast majority of women likely to have low BMD and are effective in substantially decreasing the need for all women to undergo DXA testing.[23] Weight, strongly associated with osteoporosis both in the general population[24 25] and the RA population,[1 2] is included in different decision rules for referring postmenopausal women for bone densitometry,[16 17] but is not included in the proposed criteria by Lems and Dijkmans.[8] We have previously developed a clinical algorithm to identify patients with RA at high risk for osteoporosis.[13] In this algorithm model including age, body mass index, deformed joint count, MHAQ, DAS, current use of corticosteroids, and history of non-vertebral fracture, osteoporosis was predicted with a sensitivity of 50%–60% and specificity of 80%–90% depending on the different BMD measurement sites. However, this algorithm is complex, which limits its use in daily clinical practice.

There is a significant association between corticosteroid use and BMD reduction in patients with RA.[1 10 11 15] The criteria by Lems and Dijkmans were intended to be used for patients with RA not taking long term corticosteroids.[8] Separate guidelines have been published for patients on long term corticosteroid treatment, recommending that DXA measurement is performed in all these patients.[7] In our study among the 125 (44%) patients with RA currently using corticosteroids (median duration 78 months) only 42 (34%) had osteoporosis either at the femoral neck or lumbar spine. This emphasises that not all patients taking corticosteroids long term do have osteoporosis, as also emphasised by Thompson et al[26] examining postmenopausal women using long term corticosteroids. In an attempt to develop clinical decision rules for all patients with RA independent of corticosteroid use or not, we tested a five item set of criteria including weight and ever corticosteroid use and achieved a sensitivity of 82% for women and 83% for men (table 4). Our proposed five item set of criteria may be an efficient and practical tool to select patients for DXA measurement to diagnose osteoporosis. Because of issues related especially to the availability of DXA equipment and costs, the use of DXA to diagnose osteoporosis in patients with RA should be based on a case finding strategy using validated clinical decision rules.

We conclude that the novel five item criteria, which can be applied to any patients with RA, will identify most patients with RA who have osteoporosis. The clinical decision rules provide a practical tool for doctors to identify patients with RA who should have a DXA measurement performed for diagnostic purposes. Before a final conclusion can be drawn the proposed five item set of criteria has to be validated in an outpatient population.

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Authors' affiliations
G Haugeberg, R E Ørstavik, T Uhlig, T K Kvien, Oslo City Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
J A Falch, Department of Internal Medicine, Aker Hospital, Oslo, Norway
J I Halse, Osteoporosis Clinic, Oslo, Norway

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