

Fractures and rheumatoid arthritis: frequency and clinical assessment of associated risk factors in Chinese patients.

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Abstract

Background and aim: To determine the frequency of vertebral and non-vertebral fractures in Chinese male patients with Rheumatoid Arthritis (RA) and to evaluate the associated risk factors.

Materials and methods: A total of 798 men with RA were included in this prospective cohort study from August 2009 to September 2014. Patients were categorized based on vertebral fracture, non-vertebral fracture and no fracture. The risk factor associations were evaluated by proportional hazards models.

Results: The analysis showed 1.07 fold increase in non-vertebral fractures with age (Hazards Ratio [HR], 1.07; confidence interval [CI] 1.02 - 1.16), 0.6 fold with CRP levels (HR, 0.61; CI 0.39 - 0.97), and 6.04 fold with total knee replacement [TKR] history (HR, 6.04; CI 1.16-29.90). With regards to vertebral fractures, 1.16 fold increase with age (HR, 1.16; CI 1.00-1.30), 3.32 fold with orthopedic surgery history (HR, 3.32; CI 1.66-8.12) and 7.62 fold with Chinese Health Assessment Questionnaire (HAQ) score (HR, 7.62; CI 2.66-28.90) was noted.

Conclusion: Age, low CRP levels and TKR history were found to be risk factors for non-vertebral fractures whereas age, history of orthopedic surgery and high Chinese HAQ scores as risk factors for vertebral fracture.

Keywords Fractures, Men, Osteoporosis, Rheumatoid arthritis, Risk factors.

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Introduction

Rheumatoid arthritis (RA) causes detrimental effects on bone health. RA is a chronic autoimmune inflammatory disease distinguished by extensive involvement of the synovial membrane. When aggravated, the synovial discharges cytokines that cause cartilage, fair-articular and bone loss. RA influences the joints, fibrous and connective tissues, tendons and muscles. It inclines to strike amid the adulthood, between 20 and 40 years of age, and is a chronic debilitating condition causing agony and deformation frequently. The prevalence ranges between 0.3% and 1% worldwide and is seen mostly in female and in developed countries. More than half of patients from developed countries can't hold down a full-time work within 10 years of RA onset [1,2].

Fractures constitute significant source of incapacity and diminished quality of life (QoL) in men as well as women [3]. RA patients have an increased risk of osteoporosis with respect to controls [4-7]. Also, numerous patients with RA get corticosteroid therapy to suppress inflammation, which is known to raise fracture risk. Furthermore, the oral glucocorticoids relative contribution and the underlying process of inflammatory disease to any raised fracture risk

remain unclear [8-14]. Many clinical factors should be identified to foresee risk of fractures. The identification of people at increased risk is essential in light of the fact that bisphosphonates were recorded to avert vertebral fractures in male on glucocorticoid therapy [15,16]. There is a dearth of studies focused on risk factors for fractures in male with RA. Studies conducted by Lewis CE et al. and Furuya T et al. showed age, fall/fracture history, antidepressants usage, depression, disability in walking, total knee replacement (TKR) history, serum C-reactive protein (CRP) levels etc as indicators of non-vertebral fractures in RA men [17,18].

As per our knowledge none of the studies focused on determination of the incidence and clinical features of fractures in Chinese male patients with RA. The present study objectives were to determine the frequency of vertebral and non-vertebral fractures in Chinese male patients with RA and to evaluate the associated risk factors.

Materials and Methods

This prospective single center cohort study was performed in the rheumatology department of a tertiary hospital, China over a period of five years from August 2009 to September 2014.

The study target population included all male patients diagnosed with RA (as per categorization by the American college of rheumatology (1987) [19]) and treated at the hospital. The study got the approval from the Ethics Committee and patient confidentiality was strictly maintained. Informed consent was obtained from all the patients. Chinese Health Assessment Questionnaire-Disability Index (HAQ) was used for study purpose. The patients were followed up from 6 to 60 months (from February 2010 to September 2014). Only those fractures that were reported for the first time by patients and those due to nominal trauma were included for analysis. Every male patient was categorized into groups of vertebral fracture, non-vertebral fracture and no fracture, respectively as per the status of incident fractures. The baseline clinical and demographics variables obtained were as follows: age, weight, height, body mass index (BMI), smoking and alcohol intake, rheumatoid factor (RF), duration of RA, RF positive, Chinese HAQ scores, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), physician global visual analogue scale (VAS), patient global VAS, patient pain VAS, tender joint and swollen joint count (45 joints), prior fracture history, history of orthopedic surgery or total knee replacement (TKR), and the usage corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), and osteoporosis drugs etc.

Clinically perceived events of non-vertebral as well as vertebral fractures were identified from the questionnaire. Patients were enquired regarding fractures at arm, ankle, hand, shoulder, clavicle, wrist, elbow, hip, pelvis, knee, leg, foot, nose, rib, lumbar spine, and thoracic spine biannually from August 2009 to September 2014. Then the patients were requested to mention if the fracture was due to accident, fall, sports injury, or just a spontaneous event. Based on medical and lab records reported fractures were verified accordingly. Patients were excluded if the reported fractures were unverifiable and if they are consequences of major trauma/traffic accident.

Values are expressed as numbers and percentage as well as mean with standard deviation (SD). The associations of risk factors were evaluated by proportional hazards models along with time-dependent covariates (for hazard ratio [HR] and 95% confidence interval [CI]), with adjustment for risk factors. The proportional hazards assumption was confirmed through complementary log-log plot. Mann-Whitney U test and Fisher's exact test was used for determination of statistical significance wherever applicable. Analysis of all data collected was done using R statistics software. P value ≤ 0.05 was regarded as significant statistically.

Results

Altogether, 1126 male RA patients took part in this study amid the reporting period, out of which 76 (6.75%) patients reported fractures whereas none was reported by 1050 (93.25%). Complete follow-up was done in 59 (77.6%) patients with fractures and 843 (80.29%) patients without fractures. Out of 59 patients with fractures and full follow-up, 35 (59.32%) patients were excluded due to unverifiable fractures from

medical and lab records (n=32) and motor accident (n=3). Sixty nine (8.18%) patients out of those with full follow-up and without fractures were excluded due to incomplete data.

A total of 798 men with RA were included the study. The clinical/demographic characteristics of Chinese men with RA including age, weight, height, BMI, smoking and alcohol intake, RF, duration of RA, CRP, ESR, physician global VAS, patient global VAS, patient pain VAS, tender joint and swollen joint count (45 joints), prior fracture history, history of orthopedic surgery and TKR are presented in Table 1. Drug utilization during the reporting period is presented in Table 2.

Table 1. Clinical/Demographic Characteristics of Chinese Men with Rheumatoid Arthritis (RA).

Characteristics	Fractures			P value ^a
	None (n=774)	Vertebral (n=5)	Non-vertebral (n=19)	
Age in yrs*	56.8 (13.2)	67.9 (3.6)	65.4 (6.9)	<0.001
Weight in kg*	64.8 (11.6)	58.9 (6.7)	59.5 (8.6)	0.023
Height in cm*	165 (6.4)	161 (4.6)	163 (5.9)	0.685
BMI in kg/m ² *	22.4 (3.1)	21.9 (3.2)	21.6 (3.9)	0.472
Smoking [†]	116/774 (14.9%)	1/5 (20%)	4/19 (21.1%)	0.077
Alcohol intake [†]	342/774 (44.2%)	3/5 (60%)	10/19 (52.6%)	0.062
RA duration in yrs*	7.2 (8.6)	11 (6.9)	9.2 (5.9)	<0.001
RF in IU/mL*	181.2 (276.6)	214.2 (314.1)	234.3 (301.2)	0.068
RF positive [†]	612/774 (79.1%)	5/5 (100%)	17/19 (89.5%)	<0.001
Chinese HAQ score*	0.6 (0.5)	0.8 (0.9)	0.9 (0.7)	<0.001
CRP in mg/100 mL*	1.5 (2.1)	1.7 (1.5)	1.6 (1.7)	<0.001
ESR in mm/h*	33.2 (24.5)	28.2 (19.8)	34.4 (27.2)	0.082
Physician VAS (cm)*	2.3 (2.1)	2.9 (2.8)	3.1 (2.3)	0.454
Patient global VAS*	3.1 (2.6)	2.9 (1.6)	3.5 (2.6)	0.233
Patient pain VAS*	3.2 (2.5)	3.0 (1.5)	3.6 (2.8)	0.342
Swollen joint count (45 joints)*	3.3 (4.2)	0.9 (0.7)	3.6 (3.5)	0.083
Tender joint count (45 joints)*	3.5 (4.9)	1.5 (1.2)	5.6 (6.9)	0.092
Prior fracture history [†]	262/774 (33.9%)	2/5 (40%)	9/19 (47.4%)	0.068
History of orthopedic surgery [†]	146/774 (18.9%)	2/5 (40%)	4/19 (21.1%)	0.055
History of TKR [†]	52/774 (6.7%)	1/5 (20%)	2/19 (10.5%)	<0.001

BMI: Body Mass Index; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire-Disability Index; CRP: serum C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; VAS: Visual Analogue Scale; TKR: Total Knee Replacement

Values are expressed as numbers and percentage/mean with standard deviation

^aComparing patients with and without fractures

^{*}Compared using student t test; [†]compared using chi square test

Amid the reporting period, 24 (3.01%) participants experienced clinically perceived fractures. Of these men, 5 developed vertebral and 19 developed non-vertebral fractures. The most common non-vertebral fractures were ankle and hip fractures (n=3 [15.79%], each), followed by rib (n=2, 10.53%), wrist (n=2, 10.53%), forearm (n=2, 10.53%), knee (n=2, 10.53%), elbow, toe, finger, clavicle and shoulder (n=1 [5.26%], each). Vertebral fractures noted were at thoracic spine and lumbar spine (n=2 [40%], each) and both (n=1, 20%). Out

of those with new fractures, 7 patients (29.17%) experienced multiple fractures amid the reporting period.

The most common surgeries among those who underwent orthopedic surgeries were TKR (36.18%), followed by knee synovectomies (21.3%), elbow synovectomies (8.1%), total hip replacement (8.1%) and finger synovectomies (6.6%) etc.

The proportional hazards model post multiple adjustments demonstrated 1.07 fold increase in non-vertebral fractures with age (HR, 1.07; CI 1.02-1.16; P=0.002), 0.6 fold with CRP levels (HR, 0.61; CI 0.39-0.97; P=0.032), and 6.04 fold with TKR history (HR, 6.04; CI 1.16-29.90; P=0.022) (Table 3). With regards to vertebral fractures, 1.16 fold increase with age (HR, 1.16; CI 1.00 - 1.30; P=0.003), 3.32 fold with history of orthopedic surgery (HR, 3.32; CI 1.66-8.12; P=0.041) and 7.62 fold with Chinese HAQ score (HR, 7.62; CI 2.66-28.90; P=0.002) was noted (Table 3).

Table 2. Drug utilization during the reporting period.

Drugs	Fractures			P value ^a
	None (n=774)	Vertebral (n=5)	Non-vertebral (n=19)	
DMARDs	712/774 (91.9%)	4/5 (80%)	18/19 (94.7%)	0.548
Corticosteroids	482/774 (62.3%)	5/5 (100%)	9/19 (47.4%)	<0.001
Bisphosphonates	42/774 (5.4%)	1/5 (20%)	2/19 (10.5%)	0.467
Active Vitamin D3	39/774 (5.0%)	0/5 (0%)	1/19 (5.3%)	<0.001

^aComparing patients with and without fractures using chi square test

Table 3. Risk factors for fractures in Chinese men with rheumatoid arthritis (RA).

Risk factors	Fractures	
	Vertebral (n=5)	Non-vertebral (n=19)
Age in yrs	1.16 (1.00-1.30)#	1.07 (1.02-1.16)#
BMI in kg/m2	1.01 (0.78-1.32)	0.91 (0.76-1.06)
Smoking	0.89 (0.36-2.10)	0.69 (0.27-2.07)
Alcohol intake	0.66 (0.21-3.32)	1.29 (0.56-3.22)
RA duration in yrs	1.06 (0.98-1.15)	0.98 (0.92-1.04)
Chinese HAQ score	7.62 (2.66-28.90)#	1.32 (0.66-2.96)
CRP in mg/100 mL	0.88 (0.67-1.30)	0.61 (0.39-0.97)#
Physician global VAS (cm)	1.49 (0.81-2.76)	1.26 (0.86-1.82)
Patient global VAS	0.91 (0.56-1.54)	0.99 (0.68-1.38)
Patient pain VAS	0.87 (0.55-1.41)	1.04 (0.76-1.44)

Swollen joint count (45 joints)	0.52 (0.26-1.04)	1.06 (0.92-1.20)
Tender joint count (45 joints)	1.08 (0.92-1.29)	0.96 (0.86-1.07)
Prior fracture history	2.16 (0.36-15.90)	2.02 (0.86-5.12)
History of orthopedic surgery	3.32 (1.66 - 8.12)#	2.52 (0.66 - 10.06)
History of TKR	1.12 (0.88-2.87)	6.04 (1.16-29.90)#

BMI: Body Mass Index; HAQ: Health Assessment Questionnaire - Disability Index; CRP: serum C-reactive protein; VAS: Visual Analogue Scale; TKR: Total Knee Replacement. Values are expressed as hazard ratio with 95% confidence interval (all - possible risk factor model) #P ≤ 0.05.

Discussion

Our data demonstrated age, low CRP levels and TKR history as the risk factors for non-vertebral fractures whereas age, history of orthopedic surgery and high Chinese HAQ scores as risk factors vertebral fracture. The association of age with fractures was reported in many of the studies conducted in men alone or both male and female patients with RA [11,14,17,18,20]. Studies conducted by Lewis CE et al. and Furuya T et al. showed age, fall/fracture history,

antidepressants usage, depression, disability in walking, TKR history, CRP levels etc as indicators of non-vertebral fractures in RA men [17,18]. Our data is in accordance with above studies.

Study conducted in UK showed knee arthroplasty history as a risk factor for osteoporotic as well as femur or hip fractures in RA patients [14]. TKR history was found to be a risk factor for non-vertebral fractures in studies by Furuya et al. [18,21]. Patients with TKR are prone to fall, bringing about fractures owing to bone fragility [22]. Though our study confirms previous reports, further studies on BMD should have been convincing.

In spite of the fact that seriousness of RA was accounted for to be connected with lower BMD, our study uncovered low CRP levels as a risk factor for non-vertebral fracture [18,21]. Our data demonstrated that higher Chinese HAQ scores were associated with vertebral fractures. This result is in accordance with previous studies [18,21]. Significant association of HAQ scores with osteoporosis or reduced BMD was noted in many studies [5,10,23]. Besides, troubled physical movement showed a high HAQ score, might identify with falls which are fundamental drivers for fractures in patients with RA [22]. In addition, study in USA showed disability in walking as a risk factor for fracture in aged men [17]. Along these lines, our outcomes suggest that high HAQ score is one of the vital risk factor for fractures in patients with RA.

In our study, the most widely used drugs were DMARDs followed by corticosteroids, bisphosphonates and active vitamin D3 etc. We did not analyze the effects of bisphosphonates as well as active vitamin D3 as only a small number of patients took these drugs in present study. Data on inactive vitamin D3, vitamin D2, or its metabolites were not collected in present study as active vitamin D3 prescribed by physicians was used typically and also self-supplementation is uncommon. Among RA patients, fractures were found to be more prevalent in women compared to men. Similar gender predisposition was noted in a few studies [6,14,18,21,24]. Our data is in line with such reports.

Certain inherent limitations need to be considered during interpretation of the results of current study. To start with fractures were reported by patients and though verification was done, there are chances of underestimation of prevalence due to selection bias as well as information bias. We didn't investigate BMD association with fractures in present study. In addition, this single-centre study has a restricted number of patients hence the generalization of results should be made with care. We were unable to evaluate all variables and were restricted by the treating physicians with respect to completeness of or proper documentation.

Conclusion

Our data demonstrated age, low CRP levels and TKR history as the risk factors for non-vertebral fractures whereas age, history of orthopedic surgery and high Chinese HAQ scores as

risk factors for vertebral fracture. Future robust studies are needed in this area for research.

References

1. World Health Organization. Chronic rheumatic conditions.
2. Alarcon GS. Epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 1995; 21: 598-604.
3. Adachi JD, Ioannidis G, Pickard L, Berger C, Prior JC, Joseph L, Hanley DA, Olszynski WP, Murray TM, Anastassiades T. The association between osteoporotic fractures and health-related quality of life as measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int* 2003; 14: 895-904.
4. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis. Effects of low-dose corticosteroids. *Arthritis Rheum* 1993; 36: 222-228.
5. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000; 43: 2776-2784.
6. Nolla JM, Roig-Vilaseca D, Gomez-Vaquero C, Mateo L, Juanola X, Rodriguez-Moreno J, Narvaez J, Valverde J. Frequency of osteoporosis in 187 men with rheumatoid arthritis followed in a university hospital. *J Rheumatol* 2006; 33: 1472-1475.
7. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 2000; 43: 522-530.
8. Arai K, Hanyu T, Sugitani H, Murai T, Fujisawa J, Nakazono K, Kondo N, Endo N. Risk factors for vertebral fracture in menopausal or postmenopausal Japanese women with rheumatoid arthritis: a cross-sectional and longitudinal study. *J Bone Miner Metab* 2006; 24: 118-124.
9. de Nijs RN, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, ter Borg EJ, Huisman AM, Bruyn GA, van Oijen PL, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. *Rheumatology (Oxf)* 2001; 40: 1375-1383.
10. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, Frediani B, Cantatore F, Pellerito R, Bartolone S. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. *J Rheumatol* 2000; 27: 2582-2589.
11. Michel BA, Bloch DA, Wolfe F, Fries JF. Fractures in rheumatoid arthritis: an evaluation of associated risk factors. *J Rheumatol* 1993; 20: 1666-1669.
12. Orstavik RE, Haugeberg G, Uhlig T, Falch JA, Halse JI, Hoiseth A, Lilleas F, Kvien TK. Vertebral deformities in

- 229 female patients with rheumatoid arthritis: associations with clinical variables and bone mineral density. *Arthritis Rheum* 2003; 49: 355-360.
13. van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002; 136: 1-12.
 14. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 3104-3112.
 15. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, Lane NE, Kaufman JM, Poubelle PE, Hawkins F. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001; 44: 202-211.
 16. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. *Calcif Tissue Int* 2001; 69: 242-247.
 17. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E. Predictors of non-spine fracture in elderly men: the MrOS Study. *J Bone Miner Res* 2007; 22: 211-219.
 18. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Hara M, Tomatsu T, Kamatani N, Yamanaka H. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: a prospective observational cohort study. *J Bone Miner Metab* 2008; 26: 499-505.
 19. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-324.
 20. Kanis JA, Johnell O, Oden A, De Laet C, Mellstrom D. Epidemiology of osteoporosis and fracture in men. *Calcif Tissue Int* 2004; 75: 90-99.
 21. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Kobashigawa T, Ichikawa N, Tanaka E, Momohara S, Nakajima A. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: a prospective 54-month observational study. *J Rheumatol* 2007; 34: 303-310.
 22. Kaz Kaz H, Johnson D, Kerry S, Chinappen U, Tweed K, Patel S. Fall-related risk factors and osteoporosis in women with rheumatoid arthritis. *Rheumatology (Oxf)* 2004; 43: 1267-1271.
 23. Laan RF, Buijs WC, Verbeek AL, Draad MP, Corstens FH, van de Putte LB, van Riel PL. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis* 1993; 52: 21-26.
 24. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone (NY)* 2004; 34: 195-202.

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